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TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS WITH PENICILLIN: REPORT OF CASES TREATED WITHOUT ANTICOAGULANT AGENTS*

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THE attempt to cure subacute bacterial endocarditis with penicillin was a natural sequel to similar earlier efforts with the sulfonamide group of drugs, with which the results had proved successful in sporadic cases.[1] Limiting factors in the control of the infection with the sulfonamides have included the resistance of the usual causative organism, the *Streptococcus viridans,* and the toxicity of the sulfonamide compounds when administered in the large doses and long courses required to achieve prolonged bacteriostatic concentrations in the body. Although the resistance of the *Streptococcus viridans* to penicillin is generally known to be relatively high as compared with most other pyogenic cocci, inhibiting concentrations have been reasonably attainable both in vitro and in vivo. Moreover, the non-toxic nature of penicillin gave to this new drug an advantage not possessed by any other chemotherapeutic agent previously used in the treatment of this disease.

Our experience in the treatment of subacute bacterial endocarditis with penicillin is divisible into two epochs: (1) a period during the year 1942 when treatment consisted of relatively small doses and short courses with uniformly unsuccessful results and (2) the current period, beginning early in 1944, during which massive dose therapy has been applied with highly gratifying clinical effects. Because our earlier and our current experiences are so widely different, both in practice and in results, each period is presented separately in Sections I and II which follow.

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Section I. Cases Treated With Relatively Small Quantities of Penicillin

Four cases of subacute bacterial endocarditis were treated with penicillin in 1942. The clinical features, therapy and results in this preliminary group are summarized in table 1. It will be noted that the doses and courses of

Table I

Low Dose Penicillin Therapy in Subacute Bacterial Endocarditis, 1942

Patient Unit No.		J. So. B-33258	L. S. 66584	J. M. B-29573	M. M. B-34154
Sex—Age		F.—10 yrs.	F.—20 yrs.	M.—25 yrs.	F.—36 yrs.
Type Heart Disease		Congenital (i–v septal defect)	Rheumatic (mitral)	Rheumatic (aortic & mitral)	Rheumatic (mitral)
Duration S.B.E.		1 month	4 months	3.5 months	3–4 weeks
Organism Colony Counts		Strep. vir. 175–240 col./c.c.	Strep. vir. 80–200 col./c.c.	Strep. vir. 2–7 col./c.c.	Hem. Staph. alb. (Coagulase +, Mannite +) 12–40 col./c.c.
Penicillin Resistance		0.04 u/c.c.	0.005–0.01 u/c.c.	0.04 u/c.c.	0.04–>0.1 u/c.c.
Penicillin Therapy	Days Therapy	8.5	14	28	18
	Dates of Therapy	9–3–42 to 9–11–42	7–29–42 to 8–12–42	6–25–42 to 7–24–42	10–3–42 to 10–21–42
	Doses and Routes	5000 u.q. 4 hr. Intermittent Intramuscular	5000 u.q. 4 hr. Intermittent Intramuscular	5000 u.q. 4 hr. i–v for 10 days 10,000 u.q. 4 hr. i–v for 17 days	10,000 u.q. 4 hr. i–v for 13 days 10,000 u.q. 1 hr. i–v for 3 days 5000 u.q. 1 hr. i–v for 2.5 days
	Total Course	240,000 u.	440,000 u.	1,380,000 u.	1,800,000 u.
Result		During therapy fever diminished and col. counts of blood cultures fell to 32–43/c.c. Result: failure	During therapy fever diminished and cultures of blood were less heavily positive (0–62 col./c.c.) Result: failure	Fever and symptoms notably diminished during therapy but blood cultures intermittently positive. Result: failure	Blood cultures became either sterile or yielded only light growth (0–3 col./c.c.) between 10–7–42 and discharge date of 10–27–42. Result: failure
Follow-up		Died 12 mos. later	Died 3 mos. later	Died 7 mos. later	Died 6 wks. later

penicillin ranged from a daily dose of 30,000 units for eight days in one case, to one of 100,000 units for 18 days in another. The penicillin was injected intramuscularly or intravenously in fractionated doses at four-hour intervals (in one case intravenous injections were given hourly for five days). Although the result in all these four was immediate therapeutic failure and

death within a year, it is interesting to note, in retrospect, that in all there was either temporary abolition or definite decline in fever, and the blood cultures either became sterile or yielded definitely scantier growth during these short courses with relatively small doses.

Treatment employing much larger doses and longer courses was not feasible for this disease in 1942 because of the inadequacy of penicillin supplies for civilian use, and further efforts were postponed.

Section II. Cases Treated With Massive Quantities of Penicillin

Early in 1944 we resumed therapeutic investigation of subacute bacterial endocarditis, following publication of the report by Loewe, Rosenblatt, Greene and Russell,[2] of the apparent cure of seven consecutive cases. This unique result had been achieved through the use of penicillin in massive doses supplemented by heparin, and administered over prolonged periods.

Our practice in the treatment of this disease has differed from that of Loewe and his associates chiefly in the omission of heparin. This simplification permitted evaluation of the effect of concomitant anticoagulant therapy.

*Dosage of Penicillin.** The basic plan of therapy was to treat each patient with about 240,000 units of penicillin daily for three to four weeks. A larger dose or longer course might be dictated in any case by unusually high resistance of the infecting organism to penicillin in vitro, unsatisfactory serum penicillin levels or unfavorable clinical course. Each patient therefore received 5,000,000 or more units of penicillin.

Technic of Administration. The penicillin was usually given by continuous intravenous infusion maintained day and night. Intramuscular injection of 20,000 units at two-hour intervals was employed through the entire course of treatment in only one case, but occasionally served during short periods of interruption of the continuous intravenous therapy. Continuous, slow intramuscular infusions were tried for several days in a few cases largely because of experimental interest in this technic.

For the continuous intravenous infusions the daily quantity of penicillin was dissolved in not more than 1,500 c.c. of physiological saline or 5 per cent glucose solution. In the beginning the infusion flask was enclosed in an ice jacket; later, when it was apparent that the potency of penicillin solutions did not deteriorate appreciably at room temperature,[3] the cooling device was discarded with no unfavorable effects on the outcome of cases so treated.

The equipment included a gravity infusion set with a glass Murphy drip chamber, three-way stopcock and 21 gauge needle not longer than one inch. Any convenient vein in the forearm, wrist or hand (occasionally the foot or

* The penicillin was provided by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for clinical investigations recommended by the Committee on Chemotherapeutic and Other Agents of the National Research Council.

ankle) was selected as the infusion site. When hand or wrist veins were chosen, the arm was bound firmly with adhesive tape to a small padded board in such a manner as to splint only the wrist, always leaving the elbow free. When the needle was placed in a forearm (or leg) vein high enough to avoid

FIG. 1.

interference from movement of wrist or ankle, no splint was necessary (figure 1). The needle was inserted all the way to its shank, with as much of its length lying within the vein as possible. The shank and stopcock were securely fastened with adhesive tape to the skin and also to the splint if one was used.

This arrangement usually proved entirely painless and reasonably comfortable, offered relatively free use of the extremities, and permitted maxi-

mum freedom of movement of the patient in bed or chair (figure 2). Such provisions for comfort are obviously important if the patient is to endure continuous venoclysis for several weeks. With skilled venapuncture technic, the placement and retention of the needle were usually readily accomplished, cutting down on the vein was entirely unnecessary, and phlebothrombosis was rarely encountered. The three-way stopcock was convenient for taking blood,* and for clearing an obstructed needle. The infusion was usually left undisturbed for several days, often as many as five, when a completely fresh assembly was introduced and a new vein on another extremity was

FIG. 2.

cannulated. Infusion chills were rarely encountered. Regulation of the rate of infusion was accomplished by means of a simple screw-clamp † on the infusion tubing and facilitated by the transparent drip chamber, through which the drops could be watched by either the patient or an attendant. Special nursing was quite unnecessary, but we believe that the responsibility for attending to the details of the therapeutic regimen should rest upon a single interested individual or team.

Laboratory Controls. Several unequivocally positive blood cultures were a prerequisite for treatment in each case herein reported. Observations included determination of the sensitivity of the infecting organism to penicillin, and of the penicillin serum levels during therapy. The clinical course was

* Blood drawn for serum penicillin estimations was not, however, obtained through this stopcock but always by direct venapuncture of the opposite arm to avoid the erroneously high penicillin concentrations present in the infused vein.

† Recently we have found the special Tunnel Clamp of the Harvard Apparatus Co., Dover, Mass., advantageous in maintaining an even rate of flow.

followed by the usual charting of vital signs and weight, by frequent blood cultures, by periodic blood counts, urine examinations and determinations of the sedimentation rate. Other special studies included electrocardiographic and roentgenographic examinations.

Selection of Cases. Provided that the clinical syndrome of bacterial endocarditis was present and that the diagnosis was confirmed by several positive blood cultures yielding identical organisms in number greater than just an occasional colony or two per plate, the selection of cases was relatively unrestricted. During the 16 months covered by these experiments only four cases were not treated; two died shortly after admission; a third was rejected because the infecting organism was a gram negative bacillus. The fourth was an old man who refused treatment.

Presentation of Cases. Since early 1944, 12 cases of subacute bacterial endocarditis have received massive penicillin therapy; a brief summary of each case follows.

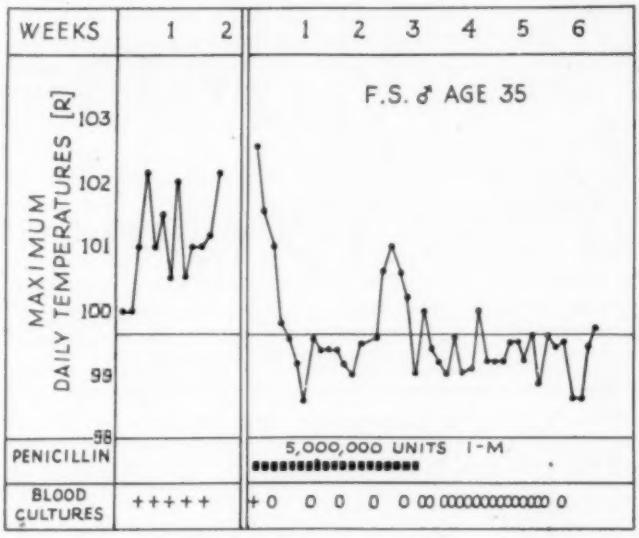
Case Reports

Case 1 (figure 3). F. S., a 35 year old barber, had no past history of rheumatic infections. He had been ill six months with weakness, fever, night sweats, a 20 pound weight loss, and evanescent pains. A bacteriological diagnosis of subacute bacterial endocarditis had been established in January 1944. The patient was in good physical condition when admitted for treatment in March 1944. He had a loud mid-systolic apical murmur, a palpable spleen, occasional petechiae, fever, increased erythrocyte sedimentation rate, moderate anemia, microscopic hematuria, and blood cultures that proved repeatedly positive for a *Streptococcus viridans* (3 to 30 colonies per c.c.) which was inhibitable by penicillin in a concentration of 0.04 unit per c.c. Treatment was with penicillin in doses of 20,000 units injected intramuscularly every two hours day and night for three weeks; the total amount given was 5,000,000 units. Petechiae, fever and hematuria soon disappeared, blood cultures promptly became sterile, and the sedimentation rate fell from 40 to 4 mm. per hour (Wintrobe method). Since termination of therapy on March 30, 1944 the patient has gained 34 pounds in weight, 30 consecutive blood cultures have been sterile, the sedimentation rate has remained normal, and there has been no clinical evidence of recurrence of bacterial endocarditis. The heart murmur has grown softer. In August 1944, 12 teeth with periapical abscesses were extracted in the course of a week without incident while penicillin was given prophylactically. The patient continues well and has been back at his work for 10 months.

This was the first case treated successfully with penicillin in our group. It was the only one in which the therapy consisted entirely of intramuscular injections.

Case 2 (figure 4). E. C., a 17 year old schoolgirl, had no past history of rheumatic infections but was known to have had a heart murmur for several years. Symptoms of bacterial endocarditis antedated hospitalization on June 23, 1944 by about 10 weeks and had consisted of fatigue, fever, a dry cough, and arthralgia of the ankles. A blood culture revealed 236 colonies of *Streptococcus viridans* per c.c. of blood. Treatment with penicillin was undertaken at another hospital where the patient was given 100,000 units daily in fractionated intramuscular injections at three to four hour intervals for 16 days without satisfactory clinical results. The patient was in

excellent physical condition when she was transferred to us, but as evidence of continuing infection there were fever, moderate anemia, microscopic hematuria, a palpable spleen, and blood cultures repeatedly positive for *Streptococcus viridans* (86 to 108 colonies per c.c.), whose penicillin inhibition level was 0.03 unit per c.c. Penicillin, given in doses of 240,000 units daily for 25 days by continuous infusion, yielded



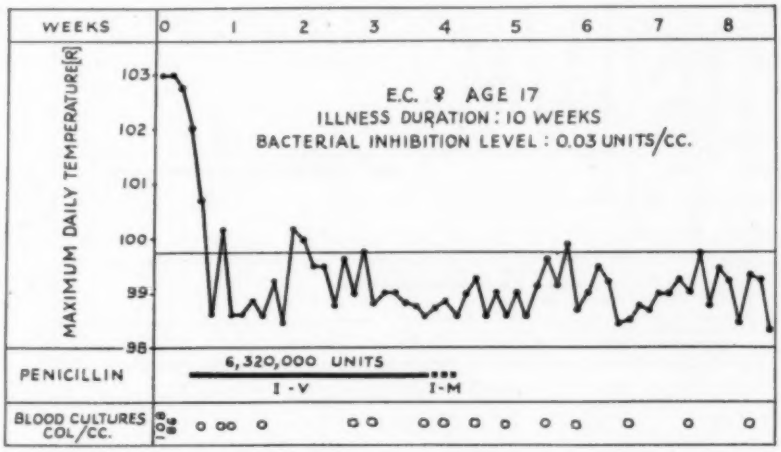
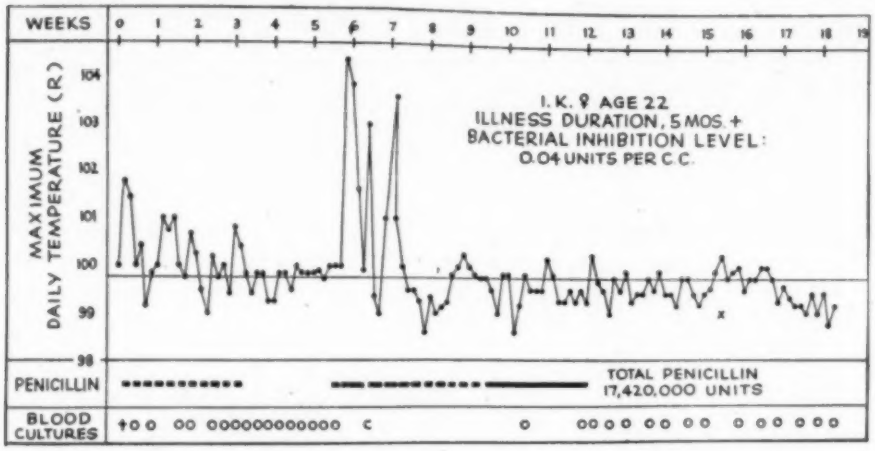


FIG. 3 (above). Case 1.
FIG. 4 (below). Case 2.

serum levels of 0.12 to 0.14 unit per c.c. The temperature declined to normal within a few days after beginning treatment, the blood promptly became sterile, the splenomegaly and the anemia disappeared, and the patient became asymptomatic. During the last week of therapy a tooth with a periapical abscess was extracted. The apical systolic heart murmur grew gradually softer and less widely transmitted. Only after four months did the sedimentation rate remain within normal limits. The patient

gained 15 pounds in weight since her illness, and all of the 16 follow-up blood cultures continued sterile. She had been at school since September 1944 and was in excellent health at the time of this report.


WEEKS
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19
MAXIMUM DAILY TEMPERATURE (R.)
104 103 102 101 100 99 98
I. K. ♀ AGE 22
ILLNESS DURATION, 5 MOS. +
BACTERIAL INHIBITION LEVEL:
0.04 UNITS PER C.C.
PENICILLIN
TOTAL PENICILLIN
17,420,000 UNITS
BLOOD CULTURES
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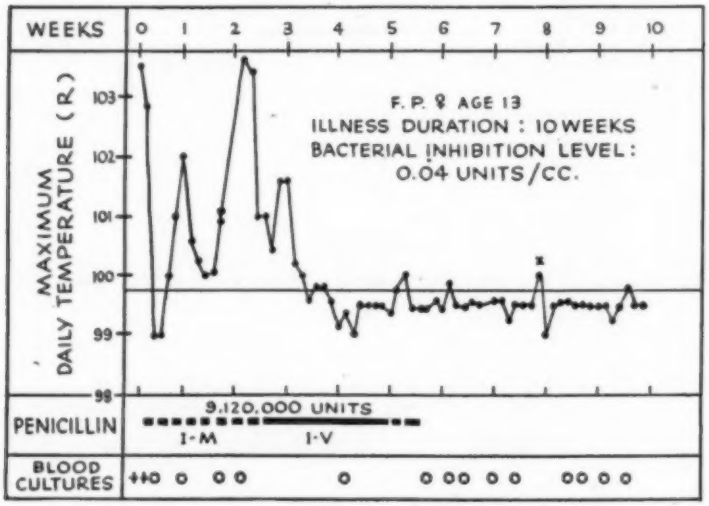


FIG. 5 (above). Case 3.
FIG. 6 (below). Case 4.

This case is particularly interesting because, in spite of the brief duration of the infection, 1,600,000 units of penicillin given by intramuscular injection during a 16 day period had failed to cure, whereas success followed a subsequent 25 day course of therapy with 6,320,000 units given by continuous intravenous drip. Satisfactory concentrations of penicillin in the blood were maintained thereby; the occasional substitution of a few intramuscular injections was definitely distasteful to the patient.

Case 3 (figure 5). I. K., a 22 year old social service worker, had had rheumatic fever at the age of 10 which resulted in mitral stenosis and insufficiency, and aortic insufficiency. Symptoms of bacterial endocarditis dated back to October 1943, and blood cultures had yielded 91 to 120 colonies of *Streptococcus viridans* per c.c. Treatment at another hospital from January to April 1944 included courses of sulfadiazine, sulfamerazine, typhoid vaccine, and repeated blood transfusions; all had been unavailing. The patient came to us on April 21, 1944 in moderately poor physical condition seven months after the onset of symptoms. At that time a few skin petechiae were noted, and the blood cultures grew *Streptococcus viridans* (50 colonies per c.c.) whose penicillin inhibition level was 0.04 unit per c.c. Penicillin was given intramuscularly in two-hourly doses of 20,000 units with prompt sterilization of the blood and a suggestive decline in temperature. The serum penicillin levels declined from 0.3 unit per c.c. at 30 minutes following injection to a mere trace at 120 minutes. Treatment was suspended at the end of three weeks for experimental reasons, although persistence of borderline fever and minor embolic phenomena argued against cure. Treatment with penicillin was, therefore, resumed. On the following day acute splenic infarction occurred. In the second course the drug was given largely by the intravenous route, with occasional interruptions and substitutions of brief intramuscular courses due to difficulties with the intravenous drip. Because of a persistent febrile and subfebrile course and increased sedimentation rate, the daily dose of 240,000 units of penicillin was raised after 21 days to 360,000 units per day, and the increased dose was maintained conservatively for 25 days longer. Therapy at this level yielded serum penicillin concentrations of 0.15 to 0.20 unit per c.c. Treatment was finally stopped on July 12, 1944, when the patient had received a total of 17,420,000 units in two courses totalling 10 weeks. Since then she has been afebrile, she has gained 30 pounds in weight, 18 blood cultures have all been sterile, and regular menstruation has returned. The sedimentation rate has always remained elevated, but this could be attributed to a mild chronic mastoiditis due to *Staphylococcus aureus*. Shortly after discharge the patient had two episodes of nocturnal dyspnea, whereupon she was digitalized. She has since remained asymptomatic and is about to resume her occupation.

Although there was no bacteriological proof that the initial three weeks of therapy with 5,000,000 units failed to cure, this conclusion seemed warranted from the unfavorable clinical course at that time. Moreover, even after three more weeks of treatment we were impelled to continue penicillin in larger doses for about three weeks longer before the desired afebrile and asymptomatic condition seemed finally established. The development of early left ventricular failure (nocturnal dyspnea) during convalescence suggested that the aortic valve had suffered increased damage as a result of the infection; digitalization and unusually long restriction of physical activity seem to have controlled this complication.

Case 4 (figure 6). F. P., a 13 year old schoolgirl, had had rheumatic fever at the ages of 8 and 10 and had developed mitral stenosis and insufficiency. The symptoms of subacute bacterial endocarditis, which included minor embolic phenomena, had begun about five months before hospitalization on May 16, 1944. The patient had lost 15 pounds in weight, and her physical condition on admission was only fair. She had a hypochromic anemia (hemoglobin 10 gm.), leukocytosis (17,000 cells/cu. mm.) and persistent microscopic hematuria. Blood cultures yielded *Streptococcus viridans* (25 to 80 colonies per c.c.) whose penicillin inhibition level was 0.04 unit per c.c. Treatment was begun with 240,000 units of penicillin daily in two-hourly intramuscular doses of 20,000 units; the serum penicillin levels attained ranged from 0.3 unit per

c.c. at one-half hour following injection to less than 0.05 unit at two hours. At the end of two weeks, during which the blood cultures remained sterile, the clinical response was considered poor because of occasional recurrence of petechiae, and persistence of fever, malaise, hematuria, anemia and increased sedimentation rate. At this time the mode of administration was changed to constant intravenous infusion employing the same total daily quantity of 240,000 units of penicillin which yielded serum penicillin levels of from 0.14 to 0.10 unit per c.c. Within five days fever disappeared, symptomatic improvement was definite, menstruation returned after six months of amenorrhea, hematuria ceased, and the sedimentation rate declined toward normal. After 22 days of intravenous therapy the penicillin was discontinued on June 22, 1944. The patient had received a total of 9,120,000 units. She was gradually mobilized at the end of two uneventful weeks and discharged a month following termination of treatment. She gained 23 pounds during the following several months, 22 consecutive blood cultures were sterile, and the patient returned to high school in the fall of 1944. She remained in excellent health until January 1945 when acute follicular tonsillitis developed and was followed by several weeks of fatigue and mild joint pains, but fever did not recur, weight remained constant, and blood cultures and blood counts remained normal. Tonsillectomy was performed in May, 1945, under protection of penicillin therapy given for five days.

This case offers evidence of the probable superiority of continuous intravenous infusion over two-hourly intramuscular injections of penicillin, for the prompt clinical remission we usually see with effective therapy did not occur until the change to continuous intravenous infusion was made in the third week of treatment. The recent recurrence of acute tonsillitis followed by symptoms suggesting subacute rheumatic fever was regarded as an indication for tonsillectomy.

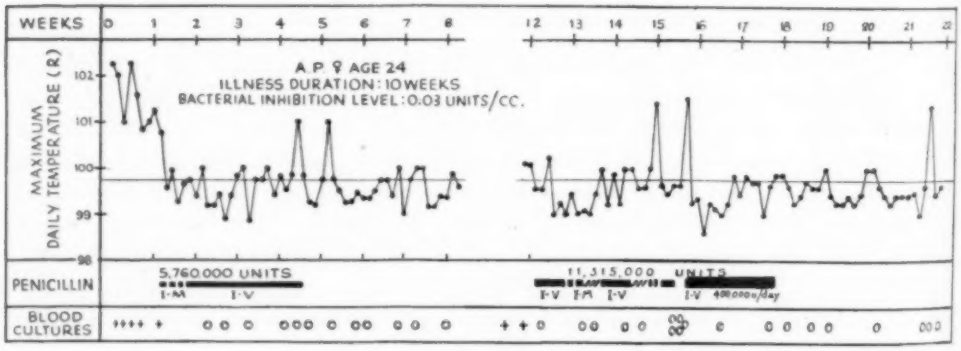


FIG. 7. Case 5.

Case 5 (figure 7). A. P., a 24 year old seamstress, had had rheumatic fever at the ages of 14 and 16 which led to mitral stenosis and insufficiency. Symptoms of bacterial endocarditis dated back only six to 10 weeks before hospitalization on August 2, 1944 and included fever, sweats, weakness and weight loss, along with petechiae and Osler's nodes. Blood cultures repeatedly yielded a *Streptococcus viridans* (25 to 87 colonies per c.c.) which was inhibitable by 0.03 unit of penicillin per c.c. Penicillin was given largely by the intravenous route for 23 days in daily doses of 240,000 units (total 5,760,000 units). The clinical response was considered satisfactory, but a few days after termination of treatment, the patient developed pain in the right

ankle, accompanied by loss of the dorsalis pedis pulse on that side, and slight fever. This was thought to be due to a non-infective embolus, for fever again disappeared and the blood remained sterile for about six weeks, although fatigue and diaphoresis continued. In the sixth and seventh post-therapy weeks fever and minor embolic phenomena reappeared, and four successive blood cultures were positive for *Streptococcus viridans* whose sensitivity to penicillin proved unchanged. Treatment was resumed, the penicillin being given at the rate of 240,000 units per day, by three different routes of administration (in order to compare the serum levels attained). Although the levels during continuous intravenous therapy ranged from 0.1 to 0.15 unit per c.c., the persistence of some malaise, occasional slight fever and minor embolic phenomena through 25 days of therapy led us to raise the daily dose to 400,000 units and to continue the course entirely by the intravenous route for 15 days longer. During this period the serum levels reached 0.3 to 0.4 unit per c.c., the clinical course seemed more satisfactory, and the sedimentation rate fell to normal and remained so through a month of further observation in the hospital during which sterility of the blood persisted. A single febrile rise two days before discharge was unexplained. After treatment was discontinued on December 8, 1944 the patient remained asymptomatic, menstruation was regular, she gained nine pounds in weight, sedimentation rate continued normal and 13 blood cultures were all sterile.

This was the only case in our group in which a patient who had been discharged as presumably well has had to return for retreatment so far. Inasmuch as the streptococcus originally obtained in her case was not preserved for comparison with the organism cultured some months later, we cannot definitely answer the question of relapse versus reinfection. We believe, however, that relapse had occurred, for the organism in both instances showed identical sensitivity to penicillin, and the clinical course following the second treatment period was characterized by subjective well being that was lacking after the initial course. The first course of 5,760,000 units should theoretically have been adequate for a patient whose physical condition was relatively good, whose infecting organism was of about average sensitivity to penicillin, and in whom the serum penicillin levels reached values several times greater than the in vitro inhibiting level for the organism. That therapy at this dosage was inadequate was implied not only by the relapse but also by the fact that repetition of this course still left doubt that cure had been effected, and it was not until the daily dose was raised approximately 50 per cent for two weeks longer that the total clinical picture assumed the aspects of cure. In the second and successful treatment period the patient received 11,315,000 units of penicillin; the total amount of drug expended was 16,995,000 units. Another simple lesson taught by this case is the irrelevance, so far as cure is concerned, of sterile blood cultures during and shortly after the period of active therapy with massive doses of penicillin.

Case 6 (figure 8). R. H., a 46 year old housewife, had rheumatic fever in 1939 but was known to have had considerable hypertension and a "murmur" since at least 1931. In June 1944 hysterectomy and incidental appendectomy were performed. Following this the patient failed to regain her health, chronic fever was noted and treated ineffectually with sulfadiazine; migrating joint pains appeared, and presently Osler's nodes also. A blood culture in September yielded *Streptococcus viridans.*

When admitted for treatment at the end of October, the patient had lost 10 pounds in weight, there were petechiae and moderate anemia, and the physical signs of aortic insufficiency were present along with evident left ventricular enlargement and blood pressure of 200 mm. Hg systolic and 110 mm. diastolic. Three successive blood cultures grew *Streptococcus viridans,* 30 colonies per c.c., which proved inhibitable by penicillin concentrations of 0.03 unit per c.c. Except for slight albuminuria and microscopic hematuria, the urinalyses were negative, specific gravity varied normally, and tests of kidney function and intravenous pyelography gave normal results.

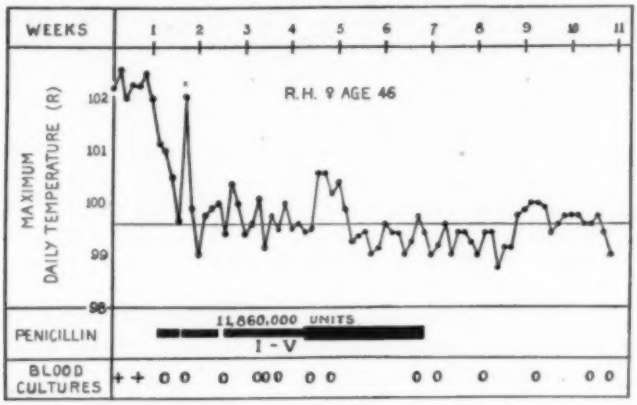
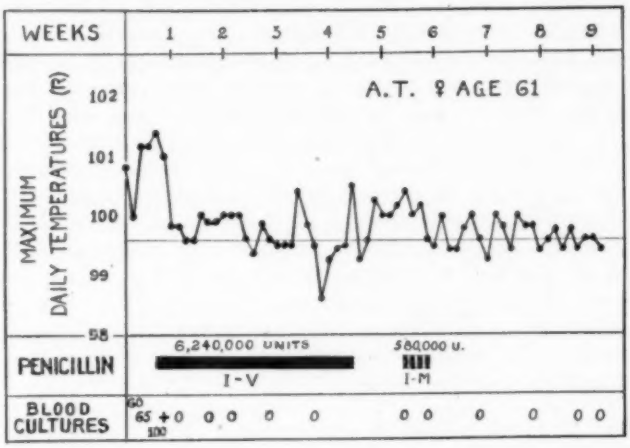


FIG. 8. Case 6.

Penicillin was given intravenously for 22 days in daily doses of 240,000 units which yielded serum penicillin concentrations of 0.08 to 0.13 unit per c.c. Because of persistence of slight fever, microscopic hematuria and increased sedimentation rate, and also because there had been no gain in weight or improvement in the anemia, therapy was continued for 18 days longer with daily doses of 400,000 units of penicillin. During the fourth week of treatment a painful swelling developed over the right mandible, fever recurred, and a presumably abscessed upper right molar tooth was extracted with prompt subsidence of fever and local signs. The course thereafter was uneventful except that the aortic diastolic murmur changed from its originally blowing character to a louder and clearly musical murmur; this musical quality continued to be present intermittently. Since termination of treatment on December 8, the patient remained afebrile and well except for apprehension about her heart. She gained 13 pounds in weight. Each of nine blood cultures was sterile, the blood count became normal, but the sedimentation rate remained slightly elevated. She gradually increased her physical activity to include the lighter household tasks.

Our chief concern in this case was the pronounced hypertension, the aortic valvular insufficiency and the indications of heart strain seen in the cardiac enlargement and the electrocardiographic pattern of left ventricular hypertrophy and strain. Moreover, there was evidence in the markedly changing character of the aortic diastolic murmur that the vegetations were situated on this valve, and one would infer that increased injury of this valve would result from the bacterial endocarditis and its healing. Because all of these factors were regarded as a threat to the existing limited cardiac reserve, we maintained full digitalization of this patient since early in her treatment

period, and we deliberately slowed her resumption of physical activity. One other detail of interest in her case was the electrocardiographic discovery of first degree A–V block (P–R 0.30 sec.). This was present before digitalization and gradually diminished to 0.22 sec. Although she had no other



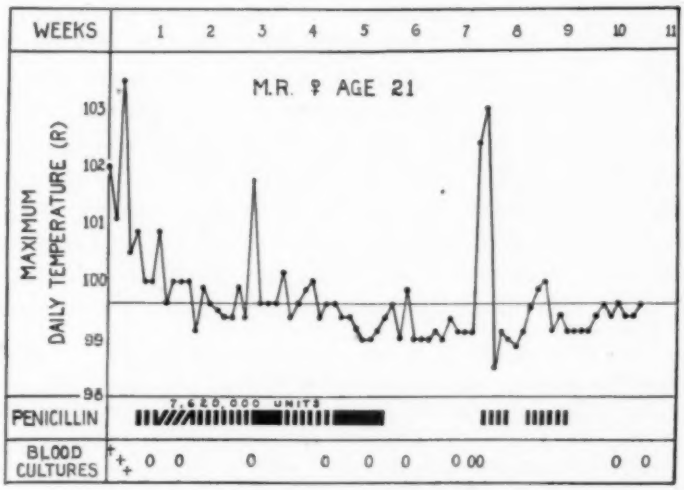


FIG. 9 (above). Case 7.
FIG. 10 (below). Case 8.

clear evidence of acute rheumatic fever, we regard this changing conduction defect as evidence of subsidence of active rheumatic carditis which has been described as a common accompaniment of subacute bacterial endocarditis.[4]

Case 7 (figure 9). A. T., the 62 year old wife of a physician, had enjoyed excellent health all her life. No heart murmurs had been detected at three routine physical examinations by two different internists over the past six years. Ill health began insidiously during October 1944 with fatigue, anorexia, declining weight and

night sweats; fever became apparent in December. Study at another hospital early in January disclosed repeatedly positive blood cultures. When transferred to us for treatment on January 11, 1945 this patient exhibited moderate fever, slight pallor, a loud, long and harsh apical systolic murmur with wide transmission, hemoglobin of 11 gm., a minimal albuminuria, and increased erythrocyte sedimentation rate. Three successive blood cultures yielded *Streptococcus viridans* (60 to 100 colonies per c.c.) whose penicillin inhibition level was 0.02 unit per c.c. Penicillin was given by constant intravenous infusion for 26 days in daily quantities of 240,000 units, with resulting serum penicillin concentrations of 0.4 unit per c.c. Fever gradually diminished after the third day, symptomatic improvement was steady, and the course was uneventful except for three minor events: a transient and superficial thrombophlebitis eight days before treatment was stopped, a tooth suspected of periapical infection was extracted early on the last day of therapy, and one week later a painful subcutaneous swelling appeared over the mandibular region on the other side accompanied by slight fever. Penicillin was given by intramuscular injection for three days, and the swelling gradually subsided in 10 days. The patient was discharged on March 15, 33 days after termination of therapy. She had received a total of 6,820,000 units of penicillin. Eight successive blood cultures since February 10 were sterile. The patient continued well, gained 10 pounds in weight, and was gradually resuming normal activity.

This patient was the oldest in our group. The etiology of the cardiac lesion that underlay the bacterial endocarditis remains obscure; although she recalled sore throats in early life, there was no past history of rheumatic fever, heart murmurs had not been heard by competent examiners prior to the present illness, and the mitral valvular endocarditis was unaccompanied by circumstantial evidence (roentgenographic or electrocardiographic) of preëxisting heart disease. Although the streptococcus concerned was quite sensitive to penicillin in vitro and the serum penicillin levels achieved were relatively high, the temperature response to therapy was not as prompt and sustained as one might have expected, and declined gradually to normal only in the post treatment weeks. However, this was counterbalanced by the surprisingly early and rapid disappearance of symptoms.

Case 8 (figure 10). M. R., a 21 year old colored housewife, had no past history of frank illness until immediately following the birth of her third child on September 7, 1944, when her right knee became painful and swollen. This condition persisted for several weeks, was followed by abdominal pain, profuse sweats and fever, and in mid-November by the appearance of pleural pain on the left side. The patient lost 20 pounds in weight through her pregnancy. When she was admitted on November 28, following a syncopal attack, she looked acutely ill, the throat was injected, the pupils were unequal, and nystagmus was observed bilaterally. The heart rate was 140 with gallop rhythm, the physical signs of mitral stenosis and insufficiency were present, and the blood pressure was 170 mm. Hg systolic and 130 mm. diastolic (hypertension gradually disappeared during the first two weeks of hospitalization). Attempts to prove a gonorrheal pelvic infection by local examinations and by cultures of the urethra and uterine cervix were unsuccessful. Three successive blood cultures were positive for *Streptococcus viridans* (3 to 6 colonies per c.c.), the penicillin inhibition level of which was 0.02 unit per c.c. Treatment with penicillin in daily quantities of 240,000 units was carried on for the first 11 days either by two-hourly intramuscular injections or by continuous intramuscular infusion. The serum penicillin levels

attained with fractional therapy ranged from 0.4 unit per c.c. in the first half hour following injection to 0.05 unit per c.c. in the fourth half hour; with continuous intramuscular infusion the concentrations of penicillin in the serum fluctuated widely as illustrated by random blood samples which yielded 0.07 to 0.26 unit per c.c. Both methods of penicillin administration, especially the intramuscular drip, proved painful and objectionable to the patient and unsatisfactory to us in the serum penicillin levels obtained. Continuous intravenous infusion of the drug was, therefore, resorted to and maintained for 22 days longer with only brief interruptions for technical reasons when intramuscular injections were substituted. With continuous intravenous administration the serum penicillin levels ranged from 0.2 to 0.26 unit per c.c. In view of progressive clinical improvement and the maintenance of a practically afebrile state during the last two weeks of therapy, penicillin was discontinued after 33 days of treatment during which a total of 7,620,000 units had been given. In the third week of convalescence an acute and severe tonsillitis developed, and penicillin injections were resumed for two and one-half days with prompt cure of the infection. A week later tonsillectomy was performed and penicillin was again resumed prophylactically for five days. Further convalescence was uneventful, and the patient was discharged on February 10, 1945. She remained asymptomatic, her weight increased 42 pounds, recent erythrocyte sedimentation rates were normal, and 15 consecutive blood cultures taken since termination of treatment on January 4, 1945 were sterile. Since discharge the original hypertension, which had disappeared during hospitalization returned, and a hypochromic anemia (hemoglobin 9 gm.) persisted in spite of prolonged treatment with iron. The cause of the anemia is obscure; urines have been persistently normal with specific gravity showing usual range of variation, and blood non-protein nitrogen has never been elevated.

This case was one of several in which we attempted to administer penicillin by constant intramuscular injection using a very slow rate of drip, but the method proved unacceptable because it was too painful, the rate of drip was relatively uncontrollable, and the resulting serum penicillin levels proved undesirably variable. Tonsillectomy was performed because the patient had had two attacks of tonsillitis during her hospitalization. We believe that tonsillar infection is a source of bacteremia and threatens reinfection of the endocardium in these vulnerable patients.

Case 9. J. S., an 11 year old schoolgirl, suffered acute rheumatic fever at the age of 7. Although a "leaking valve" developed, she observed no restraints and was largely asymptomatic until mid-November 1944, when fatigue, anorexia, sweats and ankle pains developed. Weight loss, pallor and petechiae were noted presently. Subacute bacterial endocarditis with *Streptococcus viridans* was diagnosed and confirmed by four positive blood cultures at another hospital late in December. She was given a blood transfusion, and a total of 1,000,000 units of penicillin was administered by hypodermoclysis in six days. Because fever remained high and the patient was not doing well, she was transferred to us on December 31. She looked wasted and was acutely and seriously ill, with temperature of 105° F. There were several petechiae on the extremities. The moderately enlarged heart presented gallop rhythm and a loud, harsh and widely transmitted apical systolic murmur accompanied by thrill. The spleen was palpable.

Penicillin was withheld pending the recovery of organisms from the blood for bacteriological studies. However, within the next day the temperature fell to normal and remained so for 18 days while daily blood cultures continued sterile. In view of the possibility that cure had been effected, therapy was still withheld. Meanwhile

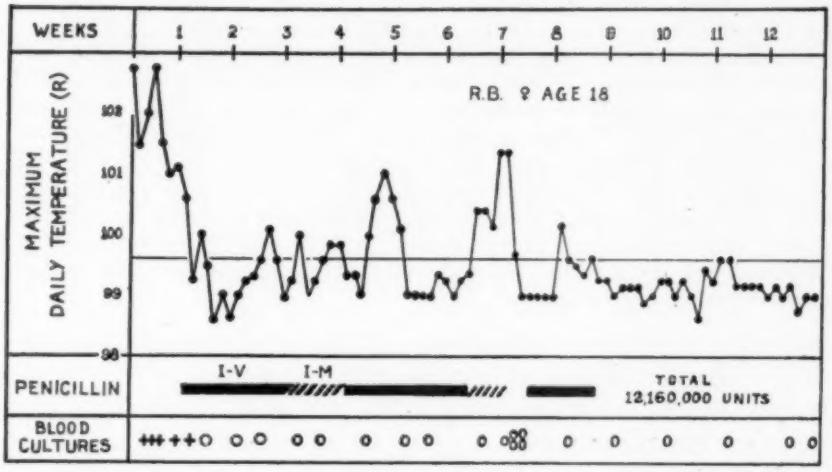
one of the original positive blood cultures was received. The organism was a streptococcus that produced green hemolysis, fermented inulin, was not soluble in bile and proved inhibitable by penicillin concentrations of 0.02 unit per c.c. During the first six weeks of observation in the hospital the blood cultures were persistently sterile, fever reappeared only once for three days in association with a lateral pharyngeal space infection, probably of dental origin, the spleen receded in size, and a few pounds of weight were gained. That the child was not well, however, was suggested by her poor general appearance, persistence of high sedimentation rate, periodic recurrence of painful petechiae and two episodes of apparent embolization of the spleen, both accompanied by severe pain. When acute pharyngitis and tonsillitis, with fever, recurred for the third time in two months, it was decided to perform tonsillectomy as a prophylactic measure, and to offer at the same time a "protective" course of penicillin in an effort to resolve the therapeutic dilemma. Accordingly, penicillin was given by constant intravenous infusion in daily doses of 200,000 units for a week prior to and two weeks following the operation, which was performed on February 28, 1945. During six weeks' observation in the hospital following termination of therapy the patient improved in general appearance, her appetite increased, she gained 12 pounds in weight, and no further petechiae or embolic phenomena appeared. Since discharge on April 21, there was no further fever, and 13 follow-up blood cultures were sterile. It was noted that the systolic murmur lost its original harshness, the systolic thrill disappeared, and a soft, low-pitched apical diastolic murmur developed.

Although we were unable to establish bacteriological proof that the patient was uncured when she was transferred to our care, it seems unlikely that six days of treatment with a total of 1,000,000 units of penicillin would have sufficed. Moreover, the patient did not appear clinically well during the two months of subsequent observation, and this was in contrast to her general clinical improvement subsequent to the tonsillectomy and the administration of 3,900,000 units of penicillin during a 20 day period. We believe the second, rather than the first, course of therapy was the curative one. The development of the murmur of mitral stenosis, together with the change in character of the systolic murmur, we regard as evidence of fibrotic healing of the vegetations on the mitral valve.

Case 10 (figure 11). R. B., an 18 year old schoolgirl, was known to have had a heart murmur since the age of 7, at which time she was confined to bed for one year. She had no cardiac symptoms and was always in good health until May 1944, when protracted illness began insidiously with headaches, malaise, weakness, fever and diaphoresis. "Pleurisy" (left side) and painful red spots on the fingers were additional incidents of this illness. She grew increasingly pale and lost 16 pounds in weight in five weeks. Following the demonstration of streptococci in the blood in July, treatment with penicillin was instituted at another hospital. Therapy consisted of three separate courses of intramuscular injections of 10,000 to 25,000 units at three and six hour intervals over a period of five and one-half weeks. She received a total of about 2,500,000 units of penicillin. Petechial phenomena persisted, and blood cultures continued to yield streptococci.

When admitted to the New Haven Hospital in September the patient looked moderately ill and was very thin and pale. There were fever and marked tachycardia. The large heart presented classical signs of mitral stenosis and insufficiency including a diastolic thrill. A cluster of petechiae was present on the chest, and the spleen was palpable. Laboratory studies revealed a moderate hypochromic anemia, a corrected

sedimentation rate of 40 mm. per hour, sinus tachycardia with a rate of 150 per minute by electrocardiogram, and aneurysmal enlargement of the left auricle by roentgenogram. Each of five successive blood cultures yielded *Streptococcus viridans* (90 to 120 colonies per c.c.) whose penicillin inhibition level was 0.03 unit per c.c. Penicillin therapy by constant intravenous infusion of 240,000 units per day was started on



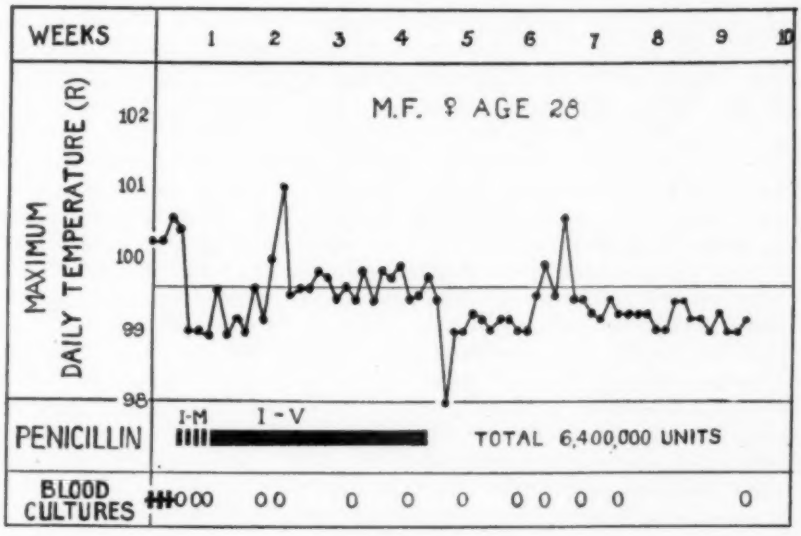


FIG. 11 (above). Case 10.
FIG. 12 (below). Case 11.

September 16. Dosage at this level yielded serum penicillin concentrations ranging from 0.2 to 0.3 unit per c.c. The temperature level fell promptly and the blood cultures remained persistently sterile after the first day of treatment. Symptomatic improvement was satisfactory and progressive, menstruation returned, no further petechiae appeared, and the patient gained several pounds in weight. However, an occasional slight febrile rise occurred, the high-grade tachycardia persisted, and

ectopic ventricular beats appeared. Although it was believed that a subacute reactivation of rheumatic fever accounted for these disturbing signs, the undeniable possibility that bacterial endocarditis was still present led us to continue penicillin. In the fifth week right ventricular failure developed. The patient was digitalized, and 5 per cent glucose in smaller quantity was substituted for saline as infusion medium. The signs of congestive failure promptly disappeared and the course thereafter was uneventful except for two episodes of fever to 101° F.; one episode was associated with a mild thrombophlebitis, the other followed a few days of administration of penicillin by continuous intramuscular infusion, which also produced severe muscle pain in the infused thigh without local or general signs of infection. Penicillin treatment was terminated at the end of 54 days, during which a total of 12,160,000 units had been given. Within the next two weeks the tachycardia subsided and the sedimentation rate fell to normal. All of 10 blood cultures taken since December 9, when penicillin treatment ceased, were sterile. The patient remained asymptomatic and afebrile, she looked very well, her blood count was normal, and she was gradually returning to a normal level of activity at home. Digitalis was being continued, although no evidence of congestive failure had reappeared.

We believe that failure of the original course of therapy which the patient had received before coming to us was attributable in part to discontinuous and insufficient treatment, and in part to the three and six hour spacing of the intramuscular injections with the result that the concentrations of penicillin in the blood were inadequate most of the time. Persistence in treatment for 54 days in this case was prompted by relatively minor evidence of continuing illness.

Case 11 (figure 12). M. F., a 28 year old colored housewife, had had acute rheumatic fever at age 13, and heart murmurs were detected two years later. The symptoms of subacute bacterial endocarditis began in October 1944, and included painful toe tips, arthralgia, amenorrhea, fever, weakness, anorexia and weight loss of 21 pounds. When admitted on January 3, 1945, the patient looked moderately ill. The classical signs of mitral stenosis were present. The spleen was not palpable but percussion dullness was increased. Three successive blood cultures were positive for *Streptococcus viridans* whose penicillin inhibition level was 0.03 unit per c.c. Penicillin was administered chiefly by constant intravenous infusion in daily quantities of 240,000 units, with which serum penicillin levels of 0.1 to 0.2 unit per c.c. were attained. During 26 days' treatment a total of 6,400,000 units was given. Except for the extraction of several abscessed teeth and for a mild febrile episode lasting two days, accompanied by pain and local swelling and tenderness of the right forearm (embolism), the course during treatment was uneventful, menstruation returned, the sedimentation rate declined to normal, and the patient gained seven pounds. During the early convalescent period there was a temporary recurrence of rheumatic fever, with mild arthralgia, slight temperature elevation, occasional ventricular ectopic beats, prolongation of A–V conduction time to 0.20–0.21 sec., and positive fibrinolysin test. The symptoms disappeared within two weeks, the P–R interval returned to the original value of 0.18 sec., and the temperature remained normal thereafter. The patient continued well, gained several more pounds in weight, and all of the 12 blood cultures obtained since termination of treatment on February 2, 1945 were sterile.

All the factors that promise therapeutic success were present in this case: brief duration of illness, good physical condition, location of the vegetations on the mitral rather than the aortic valve, a relatively sensitive infecting

organism, the ready attainment of satisfactory serum penicillin concentrations, and prompt clinical response to therapy. The presence of subacute rheumatic fever for a short time during early convalescence has been observed in two other patients in this group; the threat proved only transient in all. The finding of *Streptococcus viridans* in the sockets of several abscessed teeth confirms our impression that such foci of infection are potentially dangerous to these patients and should be eradicated.

Case 12 (figure 13). The case of D. J., a 32 year old telephone operator, has thus far been our single frank therapeutic failure. Although the patient's symptoms of migratory arthralgia, fever, weakness, headaches, anorexia and weight loss dated back only three months, she was already in very poor physical condition when she was admitted for treatment in February 1944. At this time she weighed but 80 pounds, had high fever and considerable anemia with leukocytosis. She was prostrate with severe pain apparently due to splenic infarction, the spleen was palpable, there were petechiae and Osler's nodes, and the signs of pulmonary infarction or pneumonitis were present over the left upper chest. The moderately enlarged heart presented a long and loud apical systolic murmur with wide transmission. Three successive blood cultures yielded *Streptococcus viridans* (7 to 40 colonies per c.c.) whose penicillin inhibition level was 0.05 unit per c.c. Three blood transfusions were given and on February 17 a course of penicillin was begun, which consisted of 5,490,000 units administered over 21 days in two-hourly intramuscular injections of 20,000 units each. Through this course the blood cultures remained sterile, the temperature declined steadily to normal, leukocytosis disappeared, the patient gained seven pounds, and seemed symptomatically improved. Eight post-therapy days were afebrile, but then fever gradually returned, petechiae and bacteremia recurred.

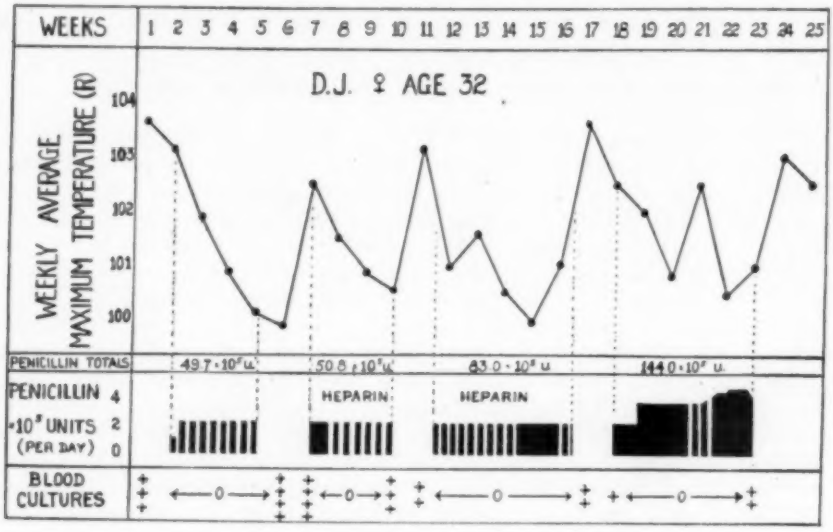
On March 23, two weeks after termination of the first course of treatment, penicillin was again resumed in daily doses of 240,000 units, and in this course we attempted to keep the coagulation time of the blood at about 30 minutes through periodic subcutaneous depositions of heparin in Pitkin's menstruum.* Again the trend of the fever was downward, the blood cultures became sterile, and during this course no petechiae appeared. However, when penicillin was discontinued at the end of three weeks, bacteremia was evident by blood culture within 24 hours, the temperatures swung quickly upward again, and petechiae reappeared.

After a lapse in therapy for nine days due to lack of penicillin, and after proving that the resistance of the organism had not changed in vitro, treatment with penicillin and heparin was resumed on April 23. In this third course, which lasted five weeks, the patient received a total of 8,300,000 units, most of which was given in two-hourly intramuscular injections, but for 11 successive days near the end of the course the administration was by constant intravenous drip. The chief event of interest in this cycle was the development of a large retinal hemorrhage and visual scotoma attributable probably to the heparin. Although the temperature course was again downward, it did not reach sustained normal levels. As in the second course of therapy, the intense local reactions produced by the subcutaneous heparin were optimistically viewed as probably causing some fever. Since the patient seemed to be improving symptomatically, appetite and weight having increased, and menstruation having reappeared, therapy was stopped on May 28. Bacteremia, renewed fever and petechiae promptly reappeared.

Because we had accomplished apparent cure in four other patients during the months of repeated failure in this case, we felt challenged to persevere in the thera-

* This material was furnished us by Dr. Leo Loewe of Brooklyn, N. Y.

peutic efforts, and some hope was found in the fact that the organism had still not increased its resistance in vitro to penicillin. The final cycle of treatment was begun on June 7. In this course continuous intravenous drip was used almost entirely because it afforded more sustained and satisfactory serum penicillin levels (0.10 to 0.14



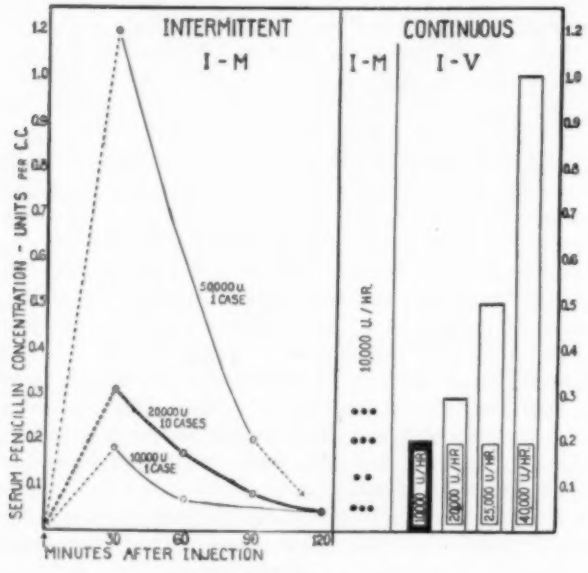


FIG. 13 (above). Case 12.
FIG. 14 (below).

unit per c.c.) than two-hourly intramuscular injections of equivalent doses. Heparin was not added. When, after five days of treatment, new petechiae still appeared, the daily dose of penicillin was increased to 400,000 units. This yielded serum penicillin concentrations of 0.3 unit per c.c. However, petechiae kept recurring and one

shower was preceded by a shaking chill and high fever. Although the blood cultures continued sterile, as usual during penicillin administration, we considered that active infection was implied, and the dose of penicillin was increased progressively to 500,000 units daily for the 11 final days. Promptly upon termination of the penicillin the temperature rose, bacteremia reappeared, and symptoms attributable to embolic phenomena returned. Family and physicians agreed that further therapeutic efforts be abandoned, and the patient was discharged. She died four months later at home; no necropsy was performed.

This patient received 32,750,000 units of penicillin during four months of active treatment. Why did failure occur in this single case? The duration of illness was no longer, the patient's physical condition was not much worse, and the infecting organism proved no more resistant to penicillin than those of other cases in this group which responded in much less time and to far smaller quantities of the drug. In retrospect, it is clear that the first and second cycles of therapy, in each of which promising signs of success occurred, were terminated prematurely when the temperature had barely reached normal. This was the first patient in the group to receive massive penicillin therapy. At that time the drug was not yet freely available, and the background of experience which should have indicated continuing penicillin instead of withdrawing it was lacking. Moreover, it had not yet been learned in the case of subacute bacterial endocarditis that with the two-hourly intramuscular injections of penicillin the serum concentration of the drug falls to undesirably low levels during the second hour, and that continuous intravenous infusion of equivalent amounts of penicillin represents more effective therapy. It seems possible that if the first course in this case had been continued for two or three weeks longer, and if the administration had been by the constant intravenous route, the result might have been as successful in this as in others. It is noteworthy that failure in this case was not due to increasing resistance of the infecting organism to penicillin, for during five months of more or less continuous administration of penicillin, the inhibition level in vitro remained unaltered.

The use of heparin in the second and third courses of treatment of this case, the only one in which anticoagulant medication was tried, did not change the outcome, and in view of the large retinal hemorrhage that appeared during heparin therapy, our feeling that anticoagulants were unimportant in the treatment, and potentially dangerous, was confirmed.

In the face of repeated failures to cure this patient, foci of infection from which bacteremia might be continuing were searched for in vain.

Summary of Cases. Of the 12 patients who received massive penicillin therapy one was a therapeutic failure and 11 are alive and well. One patient relapsed shortly after discharge; she was retreated and has been well since mid-December, 1944. At the time of this writing in June, 1945, all 11 surviving cases are under our continued observation. The time that has elapsed since termination of the treatment courses has been from one to five months in three cases, from six to 10 months in four cases, and from 11 to 15

months in another four cases. The group included one middle-aged male and 11 females ranging in age from 11 to 63 years. The etiological type of heart disease in 11 was rheumatic, in one undetermined (case 7). Ten patients had mitral valvulitis alone, one had mitral and aortic valvulitis, and one had aortic valvulitis alone; the last had marked arterial hypertension as well. Minimal congestive failure in both of the aortic and in one of the mitral cases has been kept at an asymptomatic level with digitalis and slight limitation of activity. Minor embolic phenomena occurred during therapy in most of the cases and in the early convalescent period in about one third of the cases. These occurrences did not apparently alter the successful outcome.

Streptococcus viridans was originally recovered from the blood in each case. The infecting organisms were inhibited by penicillin concentrations ranging from 0.02 to 0.05 unit per c.c., and in no case was there evidence of acquisition by the bacterium of increased resistance to penicillin.

Treatment was chiefly by continuous intravenous infusion in all cases except one who received his penicillin entirely by the fractional intramuscular route. The daily doses of penicillin ranged from 200,000 to 600,000 units per day for total periods of from three weeks to nine and one-half weeks in the cases successfully treated. No untoward effects attributable to these large quantities of penicillin were noted.

Special Laboratory Studies

Serum Penicillin Concentration and Bacterial Inhibiting Levels. Determinations of the sensitivity of the infecting organisms to penicillin and of the serum penicillin concentrations were carried out in all cases as a guide to therapy. The dose of penicillin was adjusted (from the basic minimum of 10,000 units per hour) so that the serum penicillin concentration was not less than three times the inhibiting level of the organism concerned in each case. Sensitivity assays were made at least twice on the organism obtained before therapy, and repeated on all subsequent positive cultures. Blood samples for serum concentration determinations during intravenous and continuous intramuscular treatment were drawn without preliminary adjustment of the drip rate. Hence, the levels obtained represent conditions prevailing during ordinary therapy rather than deliberately controlled experiment. Assays during intermittent intramuscular treatment were made on specimens taken every half hour for the two hours following an injection.

The sensitivity of the organisms was determined by a test tube method in which serial dilutions of penicillin in broth, each containing a drop of blood, were inoculated with the organism to be tested. A similar series of tubes, inoculated with a standard β-hemolytic streptococcus, accompanied each set of assays as a control.

Serum penicillin concentrations were determined in a similar manner, by inoculating dilutions of the serum with the standard hemolytic streptococcus.

Table 2 summarizes the serum concentrations observed in 11 of the treated cases of subacute bacterial endocarditis and four miscellaneous cases, using three modes of administration and a variety of doses. The figures recorded on each patient represent averages of several observations except for those on continuous intramuscular therapy, which are presented merely to show the wide fluctuations. Repeated assays in any one individual on continuous intravenous and intermittent intramuscular administration varied little provided the clinical conditions remained unchanged (i.e., in the absence of renal or cardiac failure). The levels obtained by the several methods of administration are compared graphically in figure 14. It is apparent that although the concentrations attained during the first hour after intramuscular injection are high, they fall off during the second hour to values probably quite ineffective in this disease. An equivalent dose per unit time given intravenously yielded a sustained therapeutic level higher than that at 60 minutes after injection. Extrapolation of the curve obtained from several observations on one patient after an injection of 50,000 units suggests that even with such massive doses no therapeutically effective amount of penicillin remains in the blood at the end of two hours.

TABLE II

Average Serum Penicillin Concentrations (Units/c.c.) in Relation to Dose and Route of Administration

	Intramuscular					Continuous Intravenous			
	Single Dose Units	Time after Injection				Units per hour			
		30′	60′	90′	120′	10,000	20,000	25,000	40,000
I. K.	20,000	0.30	0.15	0.07	T	0.18			
D. J.	20,000	0.25	0.16	0.12	0.06	0.12	0.30		
F. P.	20,000	0.30	0.13	0.08	0.05	0.12			
A. P.	20,000	0.40	0.18	0.07	0.05	0.17	0.35		
R. B.	20,000	0.30	0.20	0.05	0.05	0.25 0.40*			
M. R.	20,000	0.40	0.20	0.10	0.05	0.23			
M. F.	20,000	0.26	0.10	T	T	0.15			
M. S.	20,000	0.20	0.15	0.15	0.07	0.20	0.60†		
W. H.	20,000	0.30	0.18	0.09	0.06	0.10			
D°	20,000	0.40	0.20	0.07	0.05	0.23			
E. C.						0.13			
R. H.						0.10	0.26		
A. T.						0.40			
V. H.	50,000‡	1.2		0.20		0.17	0.23	0.50	
W. L.°	10,000‡	0.18	0.07		0.04	0.30			1.0
Avg.	20,000	0.31	0.17	0.08	0.04	0.20			

	§ Continuous Intramuscular 10,000 Units per hour						
A. P.	0.20	0.26					
M. R.	0.07	0.26					
R. B.	0.20	0.12	0.12	0.07	0.07	0.26	0.20

* In congestive failure
† In extremis
T < 0.05 u/c.c.
° Small children
‡ Not included in Average
§ Single determinations

Erythrocyte Sedimentation Rate in Relation to Therapy. Sedimentation rates were estimated periodically by the Wintrobe method to determine whether such measurements were of aid in evaluating the progress and results of therapy. These data in the 11 successfully treated cases are summarized in table 3, in which the course of each patient may be followed by its case number.

TABLE III

General Course of Corrected Sedimentation Rate

I. *Before Therapy*
   A. Abnormally Rapid Rate: All Cases.
II. *During Therapy*
   A. Persistently Normal Rate: No Cases.
   B. Sustained Trend to Normal or to Near Normal Rates: No Cases.
   C. Irregular Course Varying between Normal and Abnormal: Cases 5, 8, 11.
   D. Sustained Abnormal Rates: Cases 2, 3,* 4, 6, 7, 9, 10, 12.
III. *Early Convalescent Period (Up to 6 weeks post-therapy)*
   A. Persistently Normal Rate: Cases 1, 5.
   B. Sustained Trend to Normal or to Near Normal Rates: Cases 10, 11.
   C. Irregular Course Varying between Normal and Abnormal: Cases 2, 3,* 4, 12.
   D. Sustained Abnormal Rates: Cases 6, 7, 8, 9.
IV. *Late Convalescent Period (After 6 weeks post-therapy)*
   A. Persistently Normal Rate: Cases 1, 4, 5, 9, 12.
   B. Sustained Trend to Normal or to Near Normal Rates: Cases 2, 8.
   C. Irregular Course Varying between Normal and Abnormal: Cases 10, 11.
   D. Sustained Abnormal Rates: Cases 3* and 6.

* Chronic mastoiditis.

The sedimentation rate was always abnormally rapid before treatment, and normal values were eventually reached and maintained sooner or later in the convalescent period. It is evident, however, that the course of the sedimentation rate was entirely worthless as evidence of therapeutic success at the times when such an indicator would prove most helpful; namely, during the period of active treatment and in the early post-therapy weeks. The usual ultimate attainment of persistently normal values is simply minor corroborative evidence that the bacterial endocarditis has healed.

DISCUSSION

In contrast to the uniform failure that attended our earlier efforts to treat subacute bacterial endocarditis with small quantities of penicillin is the signal success that is now being achieved with massive doses. A successful therapeutic result in 11 of 12 cases so treated indicates that this once highly fatal disease is now probably as susceptible of cure as any other serious pyogenic infection.

In the critical examination of alleged cures in cases of subacute bacterial endocarditis, two pertinent questions arise: (1) was the diagnosis correct, and (2) was the clinical recovery a permanent condition or merely a temporary remission, either spontaneous or therapeutic? The occurrence in acute rheumatic fever and other diseases of an occasional ephemeral light bacteremia with *Streptococcus viridans* has been clearly established.[5] It is

obvious that an erroneous diagnosis of subacute bacterial endocarditis may, therefore, be made. However, the cases here presented had persistent bacteremia, usually with high or moderately high colony counts; all but one had typical embolic phenomena; all but the few very early cases had the clinical features of a wasting disease with chronic fever; and none had prominent rheumatism to suggest that the true diagnosis was merely active rheumatic fever or myocarditis. The diagnoses were based on the criteria which, from past experience, have proved sound as judged from the typically fatal course in untreated cases.

All of the discharged cases except one (case 12, who was a frank therapeutic failure) have remained well, and several who were treated early in 1944 have enjoyed approximately a year of good health. Subacute bacterial endocarditis is characteristically a chronic disease, and though usually progressive to a fatal termination within a year, remissions lasting weeks and occasionally longer are known to occur. Moreover, Libman [6] has described a bacteria-free stage of the disease. In these rather rare cases, however, clinical sequelae and evidences of continuing disease are said to characterize the course. Thus, although cures in bacterial endocarditis cannot yet be established with assurance, permanent remission is considered a probability in the foregoing cases for the following reasons. In the first place, spontaneous clinical remissions of such completeness and duration are distinctly exceptional, if known at all, rather than common in this disease, and it would make a tenuous argument indeed to contend that these successive cases happened to represent just such remarkable clinical remissions. At least, such a statistical experience has never been reported in medical literature to our knowledge. Moreover, the clinical evidences of subsidence of active infection in each of the successfully treated cases occurring usually within the first week of penicillin therapy seem more than coincidental in a chronic disease. A more plausible question than spontaneous remission is whether the disappearance of clinical signs of infection in these patients represents a temporary therapeutic remission rather than a permanent cure. Only time can answer this question, for when the therapeutic remission is regularly found to exceed a year, cure seems certainly to have been achieved. This result is already being witnessed in the first several cases presented in Section II, and in many of the patients treated by Loewe and his group.[7] Even if such cases were still viewed as therapeutic remissions rather than cures, a great advance in the control of the disease would be implied, for if a month of therapy can provide a year or more of arrest in a relentlessly progressive disease, the achievement would be worth while.

The recurrence of bacterial endocarditis after several months in any of the successfully treated cases need not necessarily indicate reactivation of the preëxisting disease, for it is not implied that successful treatment confers immunity, and reinfection is probably just as likely as ever to occur in these patients with acquired or congenital endocardial defects. Thus far we have encountered no apparent reinfection in any of our cases.

The proof of cure will also find its ultimate test when apparently cured patients die of other causes and become available for necropsy examination with careful histological and bacteriological study of the previously infected sites. That opportunity has not yet occurred in this group of patients, but a few such cases have been alluded to by others.[8, 9]

Persistent failure in the cure of subacute bacterial endocarditis has been attributed to the relative drug-resistance of the infecting organisms, the toxicity of most antibacterial drugs when administered in large doses and long courses, and the theoretical inaccessibility of the viable organisms that become safely buried in progressive thrombotic accretions. Attack upon the latter barrier has been attempted with anticoagulant agents,[2, 9, 10, 11] yet one may question the necessity of such supplemental treatment. It is conceivable that if the surfaces of vegetations can be kept sterilized for several weeks, epithelialization of the surface and fibrotic scarring of all or most of the thrombotic mass may effectively incarcerate and perhaps ultimately destroy bacteria lying beneath. That anticoagulant medication may be unnecessary was also suggested by Lichtman's statistical survey of the cures of bacterial endocarditis achieved with sulfonamide drugs.[1] The cure rate of 109 cases treated with heparin and sulfonamides was only 2.5 per cent higher than with sulfonamide compounds alone. It is noteworthy, therefore, that the use of anticoagulant agents as therapeutic supplements to penicillin has not proved necessary in the successful treatment of our cases. The maintenance of continuous heparin effect for weeks considerably complicates the technical management of these cases; the drug often causes fever which confuses the clinical course; and the administration calls for at least daily estimations of the coagulation times to guarantee proper control of the dosage. Heparin is potentially a dangerous drug, especially in a disease in which embolic phenomena are common and predispose to vascular injury with the threat of serious hemorrhage, particularly in the brain. The frequency of cerebral accidents in patients with bacterial endocarditis receiving anticoagulant medication had been repeatedly reported,[11, 12] and it is recalled that our one patient (D. J., case 12) who received heparin during two retreatment periods, developed a large retinal hemorrhage with persistent visual scotoma. Finally, heparin is expensive; the required daily amount actually costs more than the penicillin and adds hundreds of dollars to the cost of treatment of the average case. That heparin has proved unnecessary in our cases has been one of the gratifying results of our experiments. Whether heparin will prove advantageous in the treatment of far advanced cases with perhaps more massive vegetations, is yet to be learned.

In the light of current highly encouraging experience with penicillin in the control of subacute bacterial endocarditis, the consistent failures encountered earlier in our experience were obviously attributable to inadequacy of treatment in all respects: the daily doses were too small; the courses of treatment were too short; and in the use of fractional intramuscular dosage the three and four hour intervals between injections were apparently too long

for effective antibacterial titers to be maintained. With the employment of massive doses in long courses and administration of the drug by routes designed to assure sufficiently high titers of penicillin in the blood, control of the infection is proving easily attainable in most cases. Some evidence for these opinions is given in table 4.

TABLE IV

Treatment Results in Relation to Duration of Treatment and Total Quantities of Penicillin Administered

Patient	Non-Curative Courses		Curative Courses	
	Days Therapy	Total Penicillin	Days Therapy	Total Penicillin
J. So.	8.5	240,000 u.		
L. S.	14	440,000		
J. M.	28	1,380,000		
M. M.	18	1,800,000		
F. S.			21	5,000,000
E. C.	16	1,600,000	25	6,320,000
I. K.			70	17,420,000
F. P.			36	9,120,000
A. P.	23	5,760,000	40	11,315,000
R. H.			40	11,860,000
A. T.			26	6,820,000
M. R.			33	7,620,000
J. S.	6	1,000,000	20	3,900,000
R. B.	38	2,500,000	54	12,160,000
M. F.			26	6,400,000
D. J.	120	32,750,000		

Of the various modes of administration of penicillin with which we have had experience thus far, the constant slow intravenous infusion seems to have been best both from the patient's standpoint of maximal comfort, and from the scientific standpoint of maintaining relatively constant and satisfactory serum levels of penicillin with utmost economy in the use of the limited supplies available until recently.

From the technical standpoint the continuous intravenous route is admittedly not the simplest, and its successful routine use requires skillful venoclysis technic and relatively close supervision of each case during the several weeks of therapy.

A therapeutic course consisting of about 250,000 units per day for four weeks is apparently proving adequate to treat the majority of the relatively early cases in whom physical deterioration is not notably advanced, and whose infecting organism is satisfactorily inhibitable. An especially favorable case, particularly one whose infecting organism is highly susceptible to penicillin, would undoubtedly respond to less intensive treatment, whereas cases of more advanced disease and those with exceptionally resistant organisms probably demand large doses and a longer course.

Ideal control of the therapy and its proper experimental study call for bacteriological facilities permitting identification of the infecting bacterium,

estimation of its resistance to penicillin in vitro, and measurement of the serum penicillin titers obtained during treatment to assure that effective antibacterial therapy is actually being provided. It is still not known how closely the results of bacterial inhibition tests made in vitro can be translated into terms of effective serum penicillin levels required in vivo. Thus, if 0.04 unit of penicillin per c.c. of culture will inhibit growth of the bacteria in the test tube, will the administration of penicillin in amounts sufficient to yield a serum concentration slightly greater than 0.04 unit per c.c. be adequate to sterilize the blood stream and vegetations and bring about cure? In the absence of sufficient data to answer this question, and in the interest of conservative practice, an effort has been made to establish serum penicillin concentrations about three times greater than the in vitro inhibiting level of the bacterium concerned. In hospitals where ample facilities for management and study of these cases are available, the treatment of subacute bacterial endocarditis may now be considered a practical undertaking. Under circumstances where such facilities are not available and cannot be reached, treatment should not be denied but should be given empirically. The simplest therapeutic practice under such conditions would seem to be the injection of penicillin intramuscularly in doses of at least 30,000 units at intervals of not longer than two hours day and night for at least four weeks. Cure of many of the favorable cases would probably result, although the practice is admittedly wasteful of penicillin, and the occasional case harboring an unusually resistant organism would probably fail to be cured because of inadequate dosage.

Summary

Twelve patients with subacute bacterial endocarditis were treated with penicillin given in massive doses and prolonged courses. Eleven of these patients are alive and well, and in several cases more than a year has elapsed since termination of therapy.

Heparin proved unnecessary in the cure of the 11 successful cases, nor did its use alter the outcome of the single unsuccessful case.

Administration of penicillin in small doses and short courses failed to cure in all of four cases so treated in 1942.

Evidence is presented to show that of the three parenteral routes of administration employed, namely: continuous intravenous infusion, continuous intramuscular infusion, and intermittent intramuscular injections at two-hour intervals, the first was the most satisfactory.

Conclusion

Penicillin alone is an effective therapeutic agent for subacute bacterial endocarditis when the infecting organism is inhibitable by penicillin and provided that the conduct of treatment is carefully determined in each individual case.

Addendum regarding Case 10 (R. B.): On June 12, 1945, the patient was still asymptomatic, afebrile, and her blood cultures were sterile. On that day a tooth with periapical abscess formation was extracted following the prophylactic administration of a single injection of 400,000 units of penicillin-in-oil with beeswax. Two weeks later malaise reappeared with fever and positive blood cultures (*Streptococcus viridans*). Penicillin was again administered intravenously for three weeks in daily doses of 240,000 units, and the outcome was again apparent cure. On August 22 the patient was hospitalized with an acute illness including signs of meningeal infection, fever and headache. Repeated cultures of the spinal fluid and blood have remained sterile for bacteria but monilia have been grown from three cultures of the blood. All the other apparently cured cases reported above remain well at the time of this note, September 11, 1945.

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ENDEMIC (MURINE) TYPHUS FEVER: CLINICAL OBSERVATIONS OF 180 CASES *

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In the period from January 1, 1929, to December 31, 1944, 180 cases of endemic (murine) typhus fever were observed in the Charity Hospital of Louisiana at New Orleans. Although several of these cases have been previously reported,[1, 2] our observation of approximately one-half of the entire series during the past three years warrants an analysis of these cases from the clinical viewpoint.

Both European and Mexican epidemic typhus have been introduced into the United States from time to time. One of the best known instances of importation from Europe was the Philadelphia epidemic, in 1836, when Gerhard [3] successfully differentiated the disease from typhoid fever. Despite frequent occasions when epidemic typhus has been introduced into the United States this type of typhus (louse-borne) has apparently never gained a permanent foothold in this country.

Mild typhus was first observed in the United States, in 1898, by Brill [4] of New York. Recent studies by Zinsser and his associates [5] indicate that "Brill's disease" may be a late recrudescence of classic epidemic typhus in individuals who have migrated to endemic areas. Endemic typhus was first reported in the South at Atlanta, Georgia in 1913.[6] Subsequent reports [7, 8, 9] in the next few years indicated that several towns along the southern Atlantic and Gulf Coast were endemic foci of the disease. In 1923, Maxcy and Havens [10] reported a number of cases in Alabama with a positive Weil-Felix reaction. Maxcy,[11, 12] in 1926, published reports of epidemiological studies which indicated the rat to be a reservoir of infection. It remained for Dyer and co-workers,[13] however, in 1931, to separate the louse-borne typhus of Europe from the sporadic typhus of the southeastern United States by demonstrating the rat flea to be the vector, and the rat the reservoir host of these endemic cases of typhus.

Etiology

Although the Rickettsiae of murine typhus are closely related biologically to the etiologic agent of epidemic typhus, it is now recognized that two distinct varieties of the organism exist: Rickettsia prowazeki prowazeki, the etiologic agent of the classic epidemic human louse-borne disease, and Rickettsia prowazeki mooseri, the agent causing murine or endemic typhus.

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Morphologically, these two varieties of typhus Rickettsiae are identical; however, Mooser,[14] in 1928, pointed out that the virus of endemic typhus caused a pronounced scrotal reaction in guinea pigs as contrasted with the strain responsible for epidemic typhus.

The two varieties of typhus Rickettsiae, like other Rickettsiae, are small organisms showing coccoid and bacillary forms. Apparent measurements of single organisms may vary in length from 1.2 to 1.6 micra and average 0.3 micron in width.[15] These Rickettsiae have been observed in chains ranging up to 40 micra in length. Rickettsiae do not pass readily through ordinary bacterial filters. They stain poorly or not at all with ordinary methods used in staining bacteria, but can be readily stained by the special methods of Castenada, Giemsa or Machiavello.[16] Rickettsiae fail to grow in ordinary media, but are easily cultivated in the various media employing living cells, the yolk sac of the developing chick embryo being one of the preferable methods.[17]

Transmission

Endemic typhus has a reservoir in nature in the common rat, whereas epidemic typhus is transmitted from person to person by body lice (*Pediculus humanus*). The endemic variety is transmitted from rat to rat by rat fleas (*Xenopsylla cheopis*) and rat lice (*Polyplox spinulosus*). Although experiments to demonstrate the transmission of typhus by the bite of the rat flea alone have been uniformly unsuccessful, the feces of typhus-infected fleas have been found highly infectious. It would appear, therefore, that the infection is transmitted through this medium. This may take place by the rubbing of infected feces through skin abrasions, or perhaps in some instances by inhalation or ingestion.

Epidemiologic Features

As previously stated, the rat serves as the reservoir for murine typhus; however, an infected rat flea may recover from the infection and harbor the Rickettsiae for a month or more. Endemic typhus most often appears as a sporadic disease but may approach epidemic proportions, and under such circumstances transmission from man to man by the body louse is said to occur.[15, 18] The disease occurs most commonly among workers in food-handling establishments. In contradistinction to epidemic typhus, the endemic variety does not necessarily predominate among the poorer classes of people. The peak of prevalence is usually in the late summer and fall.

Endemic typhus is being recognized with increasing frequency in the United States, especially along the Atlantic and Gulf Coast, in the southern and the southwestern areas of the country.

Pathology

Gross pathologic changes include little more than the partially faded exanthem, occasionally petechial hemorrhagic lesions which may persist,

slight enlargement of the spleen, some degree of visceral cloudy swelling, and at times bronchitis and bronchopneumonia. Thrombosis of the larger vessels is rarely seen in the murine variety of typhus. The brain and meninges characteristically appear normal or present only evidences of congestion.

In 1914, Fraenkel [19] described the specific histologic lesions of typhus appearing in association with the blood vessels of the skin. Microscopically, the essential pathologic change is a generalized proliferative endangiitis, usually involving the arterioles, precapillaries, capillaries, and venules, and infrequently affecting the larger vessels. These lesions are due to growth of Rickettsiae in the endothelial cells lining the vessels. In the smaller vessels, swelling and proliferation of the affected endothelial cells may cause occlusion. Thrombosis is a result of damage to the endothelial cells of larger blood vessels. An accumulation of mononuclear cells forming small nodular lesions in the perivascular regions of smaller blood vessels is considered a characteristic feature of the disease. These lesions occur in practically all organs, but are most prominent in the brain and skin. The predominant pathologic difference between the two types of typhus is the lesser degree of extensiveness and severity seen in the endemic form of the disease.

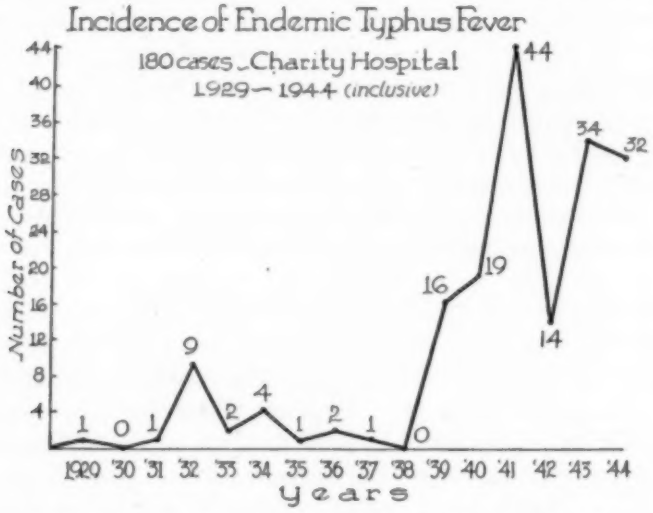
Incidence of Endemic Typhus Fever
180 cases Charity Hospital
1929—1944 (inclusive)
Number of Cases
Years
1929 '30 '31 '32 '33 '34 '35 '36 '37 '38 '39 '40 '41 '42 '43 '44
1 0 1 9 2 4 1 2 1 0 16 19 44 14 34 32

FIG. 1. Annual incidence of 180 cases of endemic (murine) typhus fever at Charity Hospital of Louisiana at New Orleans for the years 1929–1944 inclusive.

CLINICAL FEATURES

Although approximately 200 cases of typhus have been diagnosed clinically at Charity Hospital, only 180 of these were found acceptable for the diagnosis of typhus fever according to the following criteria: (1) significant or rising agglutination titers; and (2) clinical picture considered characteristic of endemic typhus. No case was included in this series unless agglutinins for OX_{19} in a titer of 1:160 or greater were demonstrated.

Incidence. As shown in figure 1, the highest incidence of typhus fever at Charity Hospital occurred in 1941, with the next greatest frequencies in 1943 and 1944. Also demonstrated in figure 1 is the increasing incidence of typhus fever since 1939. This increasing incidence corresponds to the increase in the United States as reported by the United States Public Health Service. Although the physician's attention is being focused more and more on typhus fever as a cause for obscure fevers, it is doubtful that this increase could be entirely explained on the basis of increased recognition.

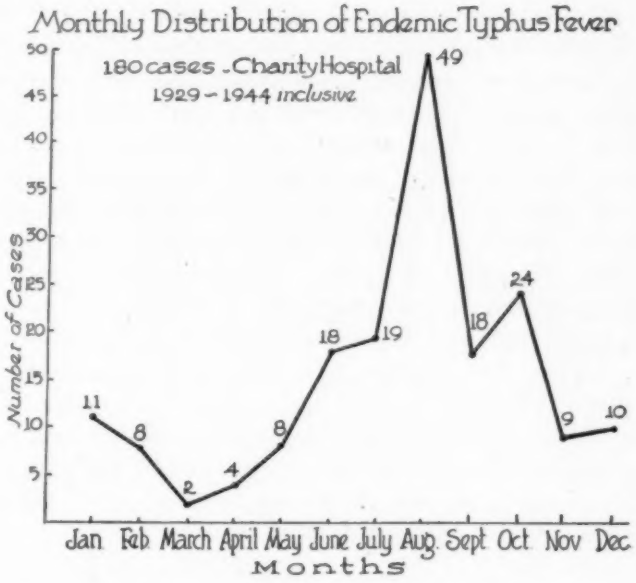

FIG. 2. Monthly distribution of 180 cases of endemic (murine) typhus fever.

As stated by others,[20] the highest incidence (figure 2) reaches its peak in the summer and early fall. Of our 180 cases, 128 (71.11 per cent) occurred from June to October inclusive, whereas the remaining 52 cases were scattered throughout the other seven months of the year.

Racial Distribution. Of the 180 cases, 129 patients were white and 51 were negroes. Although this is not directly proportional to the admissions of white and colored patients during the same period, it is quite probable that failure to observe a skin rash on many of the negro patients resulted in an incorrect diagnosis in several instances. It does not, therefore, seem justified to assume any significant differences in racial susceptibility to the disease.

Sex. There were 75 white male patients, 54 white females, 30 colored males and 21 colored females. An analysis of these data fails to reveal any significant differences in susceptibility in regard to sex, since the slight preponderance of male patients is probably due, at least in part, to occupational factors leading to contacts with the reservoirs of the disease.

Age. The average age for our group of patients was 34.6 years, which is during the peak of active life, and was probably related to the contacts of the patients of our series in many instances. The youngest patient was a white female infant said to be 20 months of age, whereas the oldest patient in this series was a colored female of 67 years.

Community Distribution. All of our patients, except one colored male who had just been released from prison in another state, were from Louisiana. This, of course, is due to the fact that the services of Charity Hospital are devoted almost exclusively to the citizenry of Louisiana and has no bearing, therefore, on the community distribution of endemic typhus elsewhere in the South. One hundred and twenty-five of our patients (69.44 per cent) were from New Orleans, whereas most of the remaining 55 were from rural communities. Fourteen (9.03 per cent) lived on farms.

Occupational Factors. The occupational groups represented in this series varied greatly. Food-handlers, including 54 housewives, comprised the largest group, 80 patients (44.44 per cent), whereas the remainder included farmers, shipyard workers, common laborers, mechanics, carpenters, plasterers and several other occupational groups. Although employees working in food-handling establishments are quite likely to contract the disease, the occupation of an individual is not necessarily associated with its development.

Contacts. Of our 180 patients, 123 (68.33 per cent) gave a suggestive history of contact. Sixteen of these had handled rats, four handled mice, and nine were of the opinion that they had recently been bitten by fleas. In each instance, a definite history of rats in the home or working environment was obtained. Thirty-four patients denied any contacts, while in 23 cases no historical data concerning contacts were available.

Dyer [16] has considered that endemic typhus may possibly have reservoirs in rodents other than the common rat. It is also generally thought that an infected rat flea may recover from the disease and harbor the Rickettsiae for four weeks or longer.[18] It would appear, therefore, that historical inquiry concerning exposure to animal contacts need not consider a wide variety of possibilities.

Incubation Period. The incubation time is said to range from five to 15 days, the usual time falling between eight and 12 days.[18, 20] Although the majority of our patients gave a history of continued or multiple contacts, there were 29 who, according to historical data, had one exposure to rats, mice or fleas. The shortest incubation period of this group was apparently four days, but one patient became ill 15 days after his exposure. Among these 29 patients, the average time required for illness to occur after exposure was 10.4 days.

Onset. Mild prodromal symptoms consisting of malaise, headache, cough, nausea, chest pain and coryza were each present in several of the 84 patients complaining of prodromata. The average duration of prodromata, which ranged from one to 10 days, was 2.7 days. The actual onset was sudden in 96 instances (53.33 per cent) and of these 79 suffered a chill in the

beginning. Other common complaints associated with the onset of illness, sudden in nature, were severe headache, marked weakness or prostration, nausea and vomiting, pains in the chest, back, limbs and abdomen. Fever was nearly always present a few hours after the abrupt onset.

Rash. The rash in endemic typhus is frequently not so pronounced as the exanthem associated with epidemic typhus, and may only comprise a few macules which disappear in two or three days. As may be seen from table 1, a rash was present in 115 cases, an incidence of 63.88 per cent. Only 10

TABLE I

Race	Rash Present	No Rash	Percentage with Rash
White	105	24	81.39
Negro	10	41	19.6
Total	115	65	63.88

of 51 negroes were observed to have a skin rash, two of these papular, whereas the remainder were maculopapular and were seen on light-skinned negroes. The rash, as observed in white patients, when seen early, was usually a pinkish macular eruption, each macule ranging from 2 to 5 mm. in diameter, which disappeared on pressure. This rash characteristically appeared on the fifth day of the disease, but was observed in some instances as early as the second or as late as the eighth day of illness. This exanthem usually originated on the trunk and spread peripherally to involve the limbs. The abdomen, chest, back, shoulders, arms and thighs were involved in the order of frequency, but the face was affected only thrice and the palms but twice. Scalp involvement was not observed. Itching was a rare complaint. The eruption was observed to fade less readily on pressure as it aged, and was more often papular, but in some instances disappeared completely in two or three days without leaving any tell-tale evidences. The duration of the rash, which varied between two and nine days, averaged six days, and usually had disappeared when defervescence occurred.

Temperature. Seventy-nine of our patients suffered a transient chill at the onset, and 48 others experienced a chill within the first 48 hours. Following the actual onset, the fever characteristically began to rise rapidly or by successive steps, usually reaching its maximum by the end of the first week. The maximum temperature recordings in our series varied from 102° F. to 106° F., but averaged 104° F. Of 127 patients who experienced chills some time during the course of their illness, 105 suffered multiple, transient chills, sometimes three or four within 24 hours. The chills recurred during a period between one and nine days in duration, with an average of 4.4 days. Only 16 of the 180 patients suffered no chills or chilly sensations during the course of their disease.

In our series of typhus patients, partial remissions of fever, usually in the mornings, were frequent during the second week of the disease. The average duration of the fever, which sometimes fell by crisis, but more characteristically by rapid lysis, was 15.6 days in this group, excluding four pa-

tients with complicating diseases. The duration varied from 12 days in one instance to 25 days in another. The duration of fever in 85 per cent of our cases, however, was between 13 and 18 days. Although defervescence by crisis was infrequently observed, an occasional case required as long as six days for lysis of the fever to occur, and the average number of days required for lysis was 3.5 days. Following this fairly rapid drop in temperature, one or more transient temperature rises during the next two or three days were not unusual, but these were of no apparent clinical significance, and did not affect the general condition, which as a rule was suddenly and greatly improved.

Neuromuscular Manifestations. Headache was usually the most prominent neurologic symptom, being present in 154 patients (85 per cent) of this series. The headache was not persistent in localization, was usually severe and not easily relieved, and often persisted throughout the illness. Although not so predominant a characteristic as in epidemic typhus, varying degrees of mental disturbance which varied from coma, stupor or lethargy, to confusion and delirium were observed. Stupor, seen in 28 instances (15.55 per cent), was the most frequent manifestation while delirium or excitement was seen 12 times and coma was present in only three cases. Nuchal rigidity was present in 10 patients. Despite the cerebral changes associated with typhus fever, which are similar to those seen in the virus encephalitides, reflex abnormalities were not present. Neurologic manifestations so severe as to suggest the necessity for lumbar puncture were present 20 times. These evidences of nervous system involvement usually cleared up rapidly with the fall in temperature associated with recovery.

Generalized muscular aches and pains were a prominent feature in 160 instances, back pain was present 138 times, marked weakness usually without actual prostration 130 times, and neck pains in 52 cases. These complaints were usually manifest early in the disease and frequently persisted until defervescence occurred.

Special Senses. Aching and soreness of the eye muscles occurred 20 times, an incidence of 11.11 per cent, while photophobia was a complaint of 30 patients (16.67 per cent). Conjunctival injection, varying in duration and severity, was present 92 times (51.11 per cent). Transient partial deafness was a complaint of five patients and tinnitus was noticed by 12 patients, five of whom received quinine therapy before entering the hospital.

Respiratory Manifestations. Some evidences of respiratory tract involvement were present in over half of this group of patients, but were not so prominent a feature as in Maxcy's series [11] of 114 cases. A characteristic short, hacking cough was present in 106 of our patients (figure 3), an incidence of 58.88 per cent. Most often the cough was non-productive, but mucopurulent sputum was raised by several, and blood-tinged sputum was produced nine times, being present in five patients with clinical and roentgenologic evidences of bronchopneumonia. Coryza, sore throat and chest pain were also frequent complaints. The most frequent respiratory sign

found was the presence of râles, usually moist, at the base of the lungs. These râles were undoubtedly a manifestation of bronchitis or bronchopneumonia in some cases, but may have been due to cardiac weakness and resulting pulmonary congestion in many others. As shown in figure 3, cyanosis was present eight times (4.44 per cent) and a friction rub was heard but once (0.55 per cent). Respirations were somewhat increased, maximum respirations recorded averaging about 30 per minute in uncomplicated cases, and markedly increased (40 or more in 10 cases) when bronchopneumonia developed.

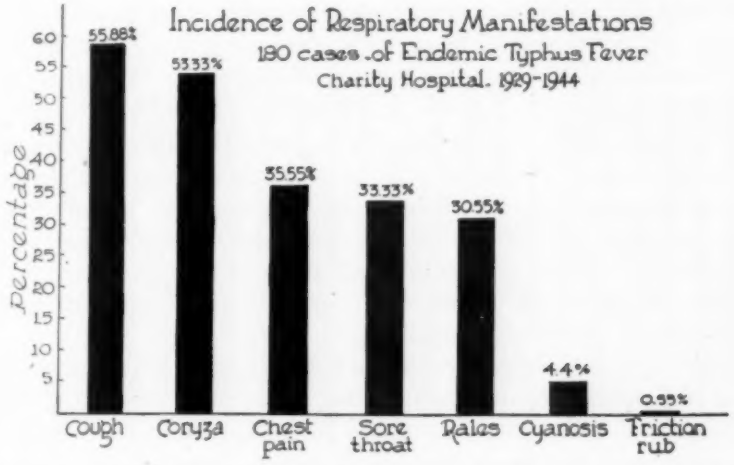

FIG. 3. Incidence of respiratory manifestations of 180 cases of endemic (murine) typhus fever.

The symptoms and signs of respiratory tract involvement were present sufficiently often to have 100 of the patients (55.55 per cent) subjected to roentgenographic examinations of the chest, several of these having two or more such examinations. Of these 100 patients, roentgenograms were considered entirely normal in 69 per cent, whereas four showed evidences of pulmonary tuberculosis which was thought to be inactive. The remaining 27 roentgenograms included 18 which were interpreted as showing signs of peribronchial thickening or hilar enlargement, while the other nine, 5 per cent of the entire series, revealed the presence of bronchopneumonia.

Cardiovascular Manifestations. Symptoms referable to the cardiovascular system were surprisingly few when one considers that the pathologic process of typhus is based on acute lesions of the blood vessels. Lowering of the diastolic blood pressure as much as 20 mm. of mercury was observed in several severe cases with evidences of marked cardiac weakness. Cardiac failure necessitating the utilization of digitalis occurred twice, one of the patients having hypertensive heart disease, and the other, 67 years of age, apparently suffering with arteriosclerotic heart disease. Although no cardiac

fatalities were observed in our series, an occasional sudden death in patients not appearing acutely ill has been reported.[11]

Venous thrombosis, occurring in the right cephalic vein, was witnessed once, and surprisingly enough did not follow the administration of intravenous medications. The pulse was subject to variations ranging between 80 and 160, the increase in rate being generally proportional to the degree of fever. The average maximum pulse rate in this series of patients was approximately 120 per minute. A dicrotic pulse was said to be present six times, an incidence of 3.33 per cent.

Gastrointestinal Manifestations. Complaints referable to the gastrointestinal tract, although quite troublesome at times, were usually of no major importance. Nausea, vomiting, or both, were present in 65 cases (36.11 per cent) and were usually more pronounced at the onset. Diarrhea varying a great deal in severity was a factor in 19 instances (10.55 per cent) whereas constipation, frequently troublesome throughout the disease, was present in 48 (26.67 per cent). Some degree of abdominal pain was present in 39 patients, an incidence of 21.67 per cent. Distention was observed in 17 patients (9.44 per cent) and tenderness on abdominal palpation was elicited on 13 occasions. The liver edge was palpable in 12 (6.67 per cent), and suspicions that jaundice was present led to icterus index determinations in 11 cases, only one of these being abnormal.

The spleen, which characteristically enlarged somewhat early in the disease, was palpable in 48 and questionably palpable in 10 others, making 58 (32.22 per cent) with spleens probably palpable. In almost every case the spleen rapidly regressed in size as clinical improvement became apparent.

Genitourinary Manifestations. Abnormalities referable to the genitourinary tract were not prominent. Nevertheless, back pains, a prominent feature of the disease when associated with chills and transient albuminuria, were responsible for a presumptive diagnosis of pyelonephritis in six cases.

Laboratory Findings

As will be shown later, about 75 per cent of these patients entered the hospital with diagnoses other than typhus fever. Consequently, this group of patients was subjected to a large number of laboratory tests. Blood cultures, consistently negative, were obtained from 137 of these patients (76.11 per cent), blood smears in a search for malaria were done 49 times (27.22 per cent), urine cultures in about one-half, spinal fluid surveys 20 times, blood urea nitrogen determinations 51 times, and blood glucose, icterus index, serum protein and other laboratory determinations were each done in several instances.

Weil-Felix Reaction. The agglutination of certain strains of the Proteus bacillus, called OX_{19} and OX_2, by the blood serum of the patient is known as the Weil-Felix reaction.[21] A total of 448 such tests was made during the illness of our 180 patients (figure 4), and it was found that the agglutinins

characteristically appeared at the end of the first week or during the second week of the disease. No tests were positive before the fifth day of illness, three of 20 being positive on that day. It was found that 95 tests failed to reveal the presence of agglutinins, the average duration of disease at the time of these examinations being 6.8 days. The average time required for the appearance of agglutinins in the titer of 1:80 was 8.5 days, 1:160 was 10.5 days, 1:320 was 11.4 days, 1:640 was 13.3 days, 1:1280 was 15.9 days, and 16.4 and 19.5 days respectively were the average duration before the appearance of agglutinins in the titers of 1:2560 and 1:5120.

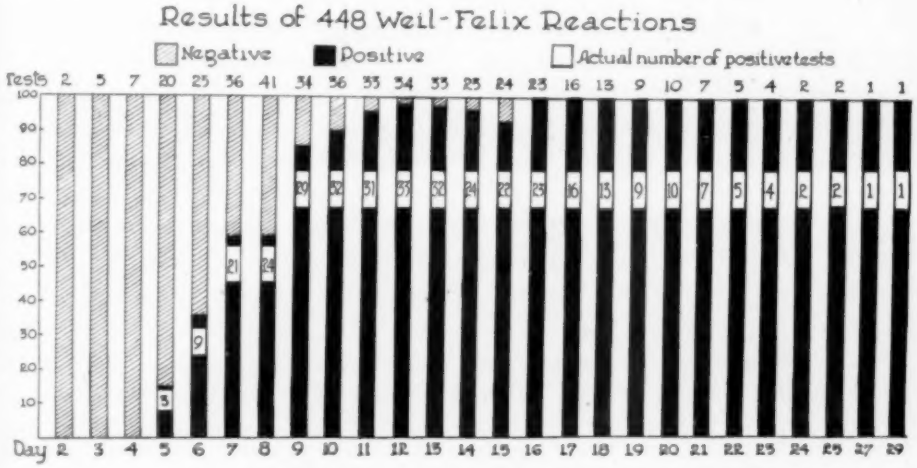

FIG. 4. Results of 448 Weil-Felix determinations. The figures at the top of each column represent the actual number of determinations performed on that particular day. The figures inserted in the heavily shaded part of each column denote the actual number of positive reactions while the percentage values are determined by the ordinates of the graph.

Although most of these cases were undoubtedly examples of endemic typhus, it is now known that Rocky Mountain spotted fever also shows a positive Weil-Felix reaction in high titers and consequently this reaction is of no practical value in differentiating between typhus and spotted fever. Recently, however, the complement fixation phenomenon, which becomes positive during the second week of the disease and may remain positive for many years, has been utilized in differentiating typhus and spotted fever.[22, 23] This phenomenon unfortunately has been utilized in few of our cases, but in one instance was responsible for establishing the diagnosis of spotted fever,[24] the Rickettsiae of spotted fever being used as an antigen.

Blood Picture. Although cellular examination of the blood is none too characteristic, it was found from an analysis of 218 white blood cell counts from our patients (figure 5) that a mild leukopenia is usually seen during the first week of the disease, and that the increase in white cells during the second week results in a mild leukocytosis. Counts ranging from 2,500 to 15,000 cells are occasionally seen in uncomplicated cases. The differential white

cell count usually fell within normal limits, and the red blood cell and hemoglobin values were apparently not affected by the disease.

Urine. Excluding two examples of chronic renal disease, the only abnormal urinary finding observed was albuminuria, which was present 30 times (17.04 per cent). This albuminuria, which usually appeared during the first week of the disease, consistently cleared up with convalescence.

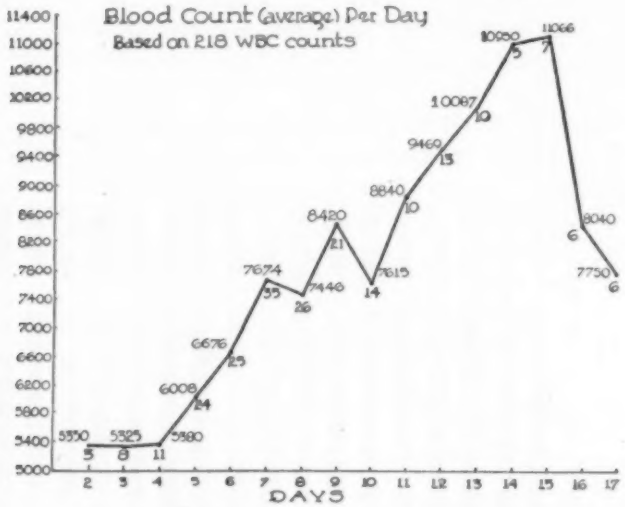

FIG. 5. The average values of 218 white blood cell counts performed on various days of illness. The figures below the curve represent the actual number of determinations on that particular day with the averaged value designated immediately above the curve.

Blood Serology. Serologic examinations were recorded in 172 instances. Four of these demonstrated positive Kline and Kolmer tests during their febrile period, these reactions becoming negative and remaining so after defervescence occurred. Thirteen patients were found to have consistently positive serologic evidences of syphilis.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

When present in epidemic form, little difficulty should be experienced in diagnosing typhus fever, but sporadic cases of the endemic type may prove more troublesome. When one bears in mind certain characteristics of the disease, it is frequently possible to entertain a presumptive diagnosis of typhus fever, especially when a contact history is obtained. An acute infectious disease, characterized by a fairly sudden onset and continuous fever of about two weeks terminating by rapid lysis is usually seen. Although a presumptive diagnosis may occasionally be made on the basis of the early symptomatology, considerable aid is obtained with the appearance of a macular rash after about five days which, in many cases, has a fairly characteristic appearance and distribution.

The routine laboratory findings, other than the Weil-Felix reaction, are not diagnostic. A mild leukopenia is usually present early in the disease, and albuminuria is observed in a small percentage of the cases. The Weil-Felix reaction, although of great diagnostic value, usually does not appear until the seventh day or later, and does not prove helpful in differentiating between endemic typhus and Rocky Mountain spotted fever.

The complement fixation phenomenon, only recently used in differentiating rickettsial diseases, which utilizes the Rickettsiae of endemic typhus fever, characteristically becomes positive during the second week of the disease, and may remain positive for many years. This test is of definite value, especially in areas where endemic typhus and spotted fever both occur.

In experienced hands, biopsies of the skin are valuable diagnostic aids. Suitable specimens may be obtained by widely excising a clearly demarcated, macular lesion, which should be fixed in Regaud's fluid and stained by the Giemsa method.[15] In typhus, Rickettsiae, if present, will be found only in the endothelial cells, whereas in Rocky Mountain spotted fever the Rickettsiae will be seen in the smooth muscle cells of the arteriolar walls.

Inoculation of male guinea-pigs and white male rats may be necessary when doubtful cases are encountered. In these instances cross immunity tests may be done. Six c.c. of blood drawn from the patient during the first week of the disease are injected intraperitoneally into each of several guinea-pigs and rats. An incubation period ranging from four to 12 days should elapse, the febrile course being observed during this period. Scrotal reactions in either animal and the development of a heavy exudate with abundance of Rickettsiae is typical of endemic typhus. Such a reaction is conclusive in the rat. Smears of scrotal cells in typhus reveal massive growth of the Rickettsiae in the cytoplasm without invasion of the nuclei. In contradistinction, smears from scrotal cells in spotted fever usually reveal a few large widely disseminated Rickettsiae in the cytoplasm, and frequent invasion of the nuclear substance. When satisfactory scrotal reactions are not obtained, immunity tests with known strains of typhus and spotted fever will usually complete the diagnosis. When an occasional atypical strain is encountered, the results of these tests may not be decisive. Under such circumstances, tissue cultures may be helpful; the extensive intranuclear growth in spotted fever is clearly seen, whereas the typhus organisms grow extensively in the cytoplasm.

Although in areas endemic to both typhus and Rocky Mountain spotted fever the final diagnosis is usually concerned with differentiating these two diseases, a large number of diseases was considered in the differential diagnosis of the 180 cases in our series. Forty-four of these cases (24.44 per cent) entered the hospital with a presumptive diagnosis of typhus fever. Other admission diagnoses are tabulated below.

Common Diagnoses

Typhoid fever	Pyelonephritis
Pneumonia	Virus pneumonia
Malaria	Measles
Influenza	Drug rash

Less Common Diagnoses

Secondary syphilis	Pharyngitis
Undulant fever	Bronchitis
Arsenical hepatitis	Sinusitis
Subacute bacterial endocarditis	Encephalitis
Cholecystitis	Cerebral concussion
Central nervous system syphilis	Infectious diarrhea
Intestinal obstruction	Poliomyelitis
Pelvic inflammatory disease	Plumbism
Meningococcemia	Tuberculosis

Although it is practically impossible to differentiate early typhus from many of these diseases, the appearance of a rash, characteristic febrile response, absence of leukocytosis, and appropriate laboratory procedures serve to eliminate most of them from the list of diagnostic possibilities. Typhoid fever, the most troublesome to differentiate, may be ruled out by blood culture, negative Widal reaction, and the different appearance and distribution of the rash. The rose spots of typhoid characteristically appear in crops, and are usually less numerous than are typhus lesions. Malaria may be eliminated by examination of blood smears, whereas the pneumonias should be excluded by roentgenologic studies of the chest. An adequate survey of the urinary tract is essential when considering pyelonephritis, while influenza and measles seldom prove troublesome for long. Drug rash, since the introduction of the sulfonamide preparations, may prove difficult to exclude, especially when a history of recent sulfonamide therapy is obtained, but discontinuing the drug frequently proves helpful if other toxic manifestations such as suppression of the urinary output or hematuria are absent.

Course

Most of the patients entered the hospital after one week of illness, but admissions varied from the first day until convalescence. The average duration of hospitalization was 15.7 days, whereas an average of 23 days elapsed between the onset at home and the day of hospital discharge. The febrile response and the rash have been described in detail. The headache as well as various other aches and pains persisted in many cases, but always disappeared before the temperature became normal.

Complications and Sequelae

Bronchopneumonia, occurring in nine of these patients, was the most common complication. Thrombosis of the right cephalic vein, possibly of no clinical significance in regard to the disease, was observed once. Only three of the patients, all in the older age group, developed bed sores. Inadequate data concerning this series of patients after hospital discharge prevent any worthwhile conclusions concerning sequelae, but some writers are of the opinion that there are no true sequelae.[15]

Prognosis

The mortality from endemic typhus in the United States as a whole is usually given as about 1 per cent.[15] Most of these deaths are said to occur in the aged. In contradistinction, the case-fatality rate during different epidemics of louse-borne typhus varies from 20 to 60 per cent.[16] There were no deaths in our series of 180 cases.

Treatment

There is no specific treatment of established value. Symptomatic and supportive measures, designed to maintain the strength of the patient, which included strict bed rest, good nursing care, maintenance of fluid balance and a liquid or soft nourishing diet with supplementary vitamins, were the basis of the therapeutic regimen in most of our cases. Occasionally a stomach tube was necessary in order to administer the necessary fluid and nutritional requirements. Digitalis was administered twice in cases showing evidences of cardiac failure. Constipation was best controlled by using enemas, whereas adequate nursing care aided in preventing bed sores. Codeine and aspirin were frequently necessary for the control of the headache; however, in many instances only minimal relief was obtained. Temperature-reducing measures such as alcohol and cold water sponge baths were employed freely. Quinine sulfate, usually 10 grains three or four times daily, was given to several of the patients with only transient effects on the febrile course of the disease. Each of the sulfonamide derivatives except sulfamerazine was given in full dosage to several of these patients before the correct diagnosis was established, the results being uniformly unsatisfactory. One patient, a white female of 28 years, received more than 700,000 units of penicillin before typhus was suspected, but no appreciable change in the course of the disease was noted. All the patients, except two deserting at the time of defervescence, were kept in bed until convalescence was well established.

From experimental work by Pinkerton and Bessey,[25] which shows that riboflavin deficiency leads to a striking and apparently specific loss of resistance to endemic typhus in the rat, it appears that the injection of crystalline riboflavin in man is perhaps indicated, particularly when a history of an inadequate diet is obtained. Pinkerton[15] has also found that the with-

holding of food following inoculation causes marked loss of resistance to experimental typhus in the guinea-pig. These observations lend emphasis to the importance of nutrition in typhus.

Recent studies by Woodward and Bland,[26] based on severe epidemic typhus in French Morocco, indicate that the circulatory collapse in typhus is mainly peripheral in origin. They demonstrated reductions in the blood volume and in blood proteins, especially albumin, and other alterations, all attributable to the vascular lesions of typhus and increased capillary permeability. They emphasize the importance of general supportive measures to restore the volume and quality of the blood. A more recent report by Harrell and his co-workers [27] on the treatment of Rocky Mountain spotted fever indicates similar findings. Thus it would appear that supportive measures should be utilized more in the treatment of conditions caused by the specific Rickettsiae.

Serum preparations are apparently of questionable value. There is experimental evidence indicating that the various sulfonamide preparations are of no value in treating typhus fever, whereas available data suggest in fact that these drugs, in experimental typhus, seem to have a deleterious effect.[28, 29] Penicillin has been found by Pinkerton and his co-workers [30, 31] to exert a beneficial effect in experimental typhus, both in mice and the infected yolk sacs of developing chick embryos. Penicillin has not yet been subjected to an adequate clinical trial, however, and it is not known whether penicillin, given early and in large amounts, will affect the course of endemic or epidemic typhus. As suggested by Yeomans and co-workers,[32] this therapeutic agent would seem indicated when evidences of secondary infection appear, especially since sulfonamide derivatives are thought to be detrimental in rickettsial diseases.

A recent report by Yeomans and his associates [32] has indicated that para-aminobenzoic acid lessens the severity and shortens the duration of louse-borne typhus. Their study, based on 20 treated cases and 44 "untreated cases," indicates that when administered properly no undesirable effects are to be expected except a tendency to develop a low white blood cell count. Although further information is needed, this therapeutic substance may also prove valuable in lessening the severity and duration of endemic typhus.

Prevention

Since the rat is the reservoir, the control of endemic typhus fever should be based on the control of the rat population. This is best accomplished by poisoning and trapping, the rat-proofing of buildings, and the disposition of garbage beyond access to rats. Of these measures, rat-proofing is the only one that may be considered as of some permanent value. Unless supplemented by this measure, trapping and poisoning must be continuous to be of any practical value.

Vaccines utilizing technics employing living cells as a medium have been prepared against endemic typhus. Immunization programs are not generally advocated, however, since the mortality rate is low and the disease occurs sporadically, usually showing little tendency to become epidemic. Dyer [16] has suggested that the vaccine might be used to advantage in the protection of those employed in food-handling establishments, but points out that one is not justified in enabling the management of such an establishment to maintain rat harborage.

SUMMARY

We have reported the clinical observations of 180 cases of endemic (murine) typhus fever occurring in the past 16 years at Charity Hospital of Louisiana at New Orleans. Almost one half of these cases have been observed, however, in the past three years and this and other data lend support to an increasing incidence of typhus fever in the southern United States. The clinical picture, diagnosis and treatment of the disease have been discussed in detail.

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THE USE OF THIOURACIL IN THE TREATMENT OF PATIENTS WITH HYPERTHYROIDISM *

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Historical Review

The origin of the use of thiouracil in the treatment of hyperthyroidism stems from the past studies of the mechanism of the production of experimental goiter. During the course of these studies in which the rôle of iodine in the production of simple goiter was convincingly demonstrated, many interesting facts were unearthed that were to be of striking importance in the development of the rationale for the use of thiourea derivatives in the treatment of hyperthyroidism.

In 1928, Chesney and his co-workers [1] noted the development of goiter in their stock rabbits fed on a cabbage diet. The thyroid glands of these animals were found to be enlarged, and microscopically they showed considerable hyperplasia with no tendency to colloid formation. This development was accompanied by a decrease in the production of body heat, the heat production varying inversely with the size of the thyroid. Iodine administered to the goiterous animal resulted in a rise in metabolic rate and a fall in body weight. It brought about, however, involution of the hyperplastic gland.

In 1930, Webster and Chesney [2] demonstrated that the administration of iodine in sufficient quantities would protect rabbits against the goitrogenic effect of the cabbage diet. Meanwhile, Marine and his co-workers [3] showed that other members of the Brassica group were also goitrogenic. The goitrogenic effect, however, was inversely proportional to its iodine content. It was, therefore, presumed that cabbage contained an agent that reduced the effective thyroxin and iodine content of the thyroids of rabbits. This resulted in hyperplasia of the gland.

Since the most important chemical constituents of the Brassicae were mustard oils, the effect of these isothiocyanates and their cyanide precursors were investigated. With acetonitrile, and other related compounds, Marine [3] was able to produce hyperplasia of the thyroids, and, in some animals, exophthalmos.

Soy bean flour was also demonstrated to be goitrogenic in rats.[5, 6] The thyroid became hyperplastic with little or no colloid. The basal metabolic rate remained unaltered. The development of goiter by this means could similarly be prevented by the use of iodine, the minimum iodine requirement

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The Thiouracil was furnished by Lederle Laboratories, Inc., Pearl River, N. Y.

being twice that necessary in normal rats. It was presumed, since soy beans are rich in cyanogens, that these latter were the goitrogenic agents.[7]

That the cyanide derivatives may have an importance in clinical medicine is emphasized by the fact that the development of goiter is not infrequent in hypertensive patients receiving thiocyanates.[8, 9] Means and his group reported the results observed in a case of hypertension treated with thiocyanates. With the development of goiter, the basal metabolic rate fell to — 17 per cent, lid lag and exophthalmos developed, and the plasma iodine content fell to myxedematous levels. Biopsy of the thyroid revealed extreme hyperplasia and vascularity. Following cessation of therapy, the basal metabolic rate and the plasma iodine level returned to normal, while the thyroid became considerably smaller.

In 1941, Richter and Clisby,[10, 11] while studying the effects of phenylthiocarbamide, found that rats fed this drug developed goiter with marked hyperplasia of the thyroid gland. No exophthalmos was noted. At about the same time (1941), Kennedy and his group [12] studied the goitrogenic agents in Brassica seeds. They found that the diet was markedly goitrogenic in rats, but unlike soy bean and cabbage diets, large doses of iodine afforded only a minimal protection against the resulting hyperplasia and hypertrophy of the thyroid.

Marked changes in the basophile cells of the pituitary gland were noted to occur in rats that had been fed soy bean flour and were similarly observed following thyroidectomy. Griesbach [12] found that the changes in the pituitary in rats fed rape seed reflected the changes in the thyroid, the basophiles increasing in number as the thyroid underwent hyperplasia, whereas the acidophilic elements accumulated when colloid storage occurred. It was concluded that the basophile changes coincided with an increased secretion of thyrotropic hormone. Kennedy and his co-workers [12] were able to show that an intact hypophysis was essential for the production of thyroid hyperplasia. Hyperplasia produced by the diet regressed after hypophysectomy, while colloid formation after hypophysectomy was not prevented by the goitrogenic diet.

Almost simultaneously, the MacKenzies and McCollum,[13] studying the effect of sulfaguanidine on the coliform bacteria in rats, noted the development of thyroid hyperplasia and hypertrophy following the use of this drug. Similar changes were noted to occur with the use of sulfanilamide and thiourea.[14]

Kennedy [15] attempted to isolate the goitrogenic agent in rape seed, and suggested that it might be a derivative of thiourea. Allylthiourea was tested and found to produce goiter in rats, with changes in the thyroid and pituitary glands similar to those seen after the ingestion of rape seed. No toxic effects were encountered.

In 1943, the MacKenzies [16] and Astwood [17] simultaneously published their results on the mechanism of the production of goiter by the sulfon-

amides and thiourea derivatives. It was shown that the thyroid underwent marked hyperplasia, that the basal metabolic rate fell, that changes like those following thyroidectomy occurred in the anterior lobe of the pituitary, and that iodine was of no avail in counteracting these changes. They could be prevented, however, by thyroid extract or by hypophysectomy. The occurrence of a lower basal oxygen consumption, the decrease in food intake, and the diminished rate of growth and development suggested a hypothyroid state.

Astwood [18] studied a large group of compounds including the sulfonamides, thiourea, and cyanides in an attempt to determine the chemical grouping responsible for the action, as well as to determine the agent with the greatest potency and least toxicity. He found that two classes of substances were active, derivatives of thiourea, of which 2-thiouracil was the most effective, and certain derivatives of aniline dyes, including the sulfonamides. Thiocyanates were found to be active only in the absence of iodine, whereas organic cyanides were without effect.

In 1943, Astwood [19] reported preliminary studies on the use of thiourea and thiouracil in the treatment of hyperthyroidism. Many reports have appeared since then dealing with the use and toxic effects of these compounds.[20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 31, 32, 33, 47, 48]

Mechanism of Action

In experimental animals, the administration of thiourea and related compounds produces a fall in the basal metabolic rate, hyperplasia of the thyroid, the appearance of "thyroidectomy cells" in the anterior lobe of the hypophysis, lessens food intake and causes subnormal growth and development.[34, 45] The experimental evidence would suggest that these substances result in a decrease in the production of thyroid hormone, possibly by interfering with the iodinization of protein. It is this reduction in the formation of thyroxin which causes a fall in the basal metabolic rate and the disappearance of the other signs and symptoms of hyperthyroidism noted clinically. The reduction in the amount of circulating thyroid hormone produces a compensatory increase in the formation of thyrotropic factor by the anterior pituitary lobe. The thyrotropic factor, in turn, induces the hyperplasia of the thyroid.

Clinical Results

We have employed thiouracil in the treatment of 51 patients with hyperthyroidism and in three patients with non-toxic goiter. This last group was admitted to the hospital for cosmetic thyroidectomies, and thiouracil was employed in order to study the effect of this drug on the histology of the thyroid.

The patients were hospitalized for a period of four to six weeks, and were subsequently followed in the Out-Patient Clinic for the duration of the

study. During their stay in the hospital, in addition to frequent basal metabolic rate determinations, careful studies of renal and hepatic function were conducted both at the beginning of thiouracil therapy and just before discharge from the hospital. Complete blood counts were performed twice a week. This procedure was continued after discharge from the hospital to the Out-Patient Clinic. Sternal marrow aspirations were performed several times on each patient during the period of observation. Blood cholesterol determinations, circulation time, electrocardiographic tracings, neck size and measurements of the degree of exophthalmos were determined once a week while the patient was in the hospital.

Liver function studies performed on each patient included the determination of the icteric index, cephalin flocculation test, galactose tolerance test, and determination of urinary urobilinogen. Renal function studies included gross and microscopic examination of the urine, determination of urine albumin and urine concentration tests.

The dosage employed varied from 0.4 gram to 1.0 gram daily in divided doses for the first four weeks during the patient's stay in the hospital. When the patient was discharged for care in the Out-Patient Department, the amount of the drug was reduced to 0.1 or 0.2 gram daily thereafter. It has been our impression in general that most patients do better when the larger doses are employed. In some instances we have obtained equally satisfactory results where smaller amounts of the drug were used. The frequency and severity of the toxic reactions are apparently in independent of the dosage of the drug employed.

The Effect of Thiouracil Therapy on the Basal Metabolic Rate, Pulse, and Weight. In all of the patients in Group A (chart 1) there occurred a fall in

CHART I

Summary of Cases Studied

A. Hyperthyroidism treated successfully with thiouracil:
   1. Primary hyperthyroidism—29 cases
   2. Recurrent hyperthyroidism—4 cases
B. Hyperthyroidism: Lack of response to thiouracil—4 cases
C. Hyperthyroidism: Cessation of therapy due to toxic reactions—11 cases
D. Hyperthyroidism: Prepared for operation with thiouracil—3 cases
E. Non-toxic goiter: Prepared for operation with thiouracil—3 cases

the basal metabolic rate, a gain in weight, and a slowing of the pulse. Subjective improvement in symptoms was usually the earliest evidence of a beneficial effect. This was noted toward the end of the first week or early in the second week of therapy. Some reduction in the basal metabolic rate frequently occurred within one week, but a definitely significant fall was generally not observed until the second or third week, and in a few instances the lag was slightly longer. Figure 1 illustrates the fall in the basal metabolic rate plotted against the time, in 10 instances. A gain in weight and fall in pulse rate accompanied the reduction in basal metabolic rate.

One of the important factors causing a delay in response in the basal metabolic rate was the previous administration of iodine, although this is not always true. Thus in case 5, who had been receiving Lugol's solution for five months before treatment with thiouracil there was a fall in the basal metabolic rate noted in two weeks with a progressive fall noticeable thereafter, especially during the fourth week and later (figure 1). How-

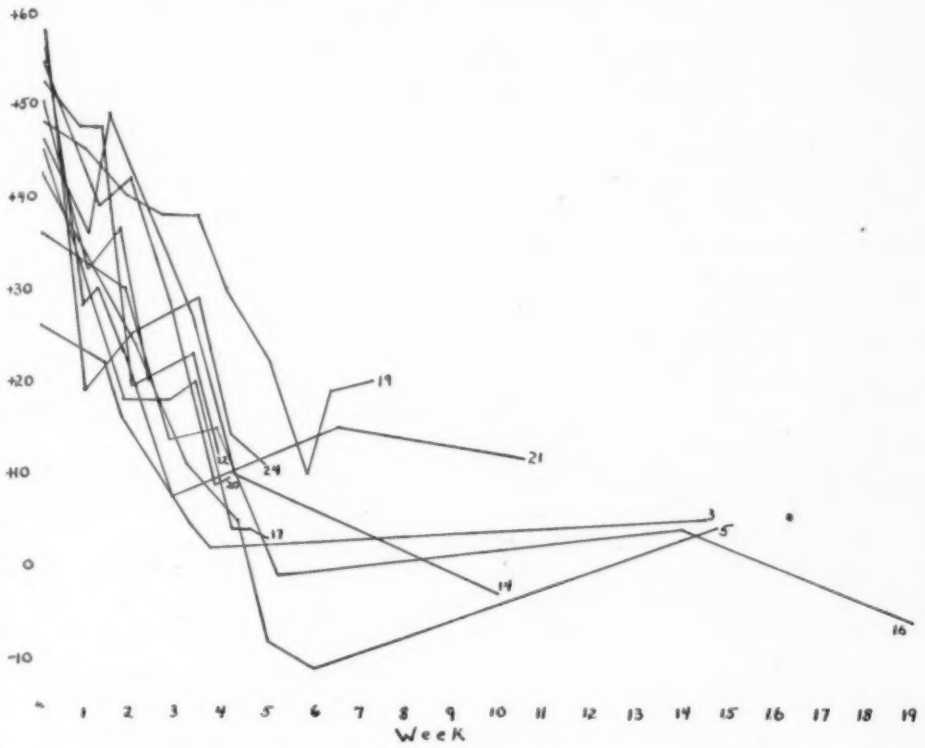

FIG. 1. The BMR-time relationship of 10 selected cases on thiouracil therapy in Group A. The numbers refer to the cases (see text.)

ever, in a second instance (case 2, figure 2) the patient had received Lugol's solution for eight months, and a moderate fall in the basal metabolic rate was noted in two weeks, but then a plateau ensued and a further fall was noted in the Follow-Up Clinic seven weeks after the onset of therapy. In a third patient (case 13) who had received Lugol's solution for three months, no effect on the basal metabolic rate was noted in the hospital after 18 days of therapy. No further determination of the basal metabolic rate was made until eight weeks after the onset of therapy, at which time there was a considerable drop. The failure of response in two cases to be discussed later, cases 38 and 39, may have been due in part to the previous use of iodine.

These effects are what one would expect from a consideration of the results of animal experiments, and are in conformity with the findings of most other observers. The object of treatment with thiouracil is either to treat the patient with hyperthyroidism until a natural remission occurs, or to continue such treatment until exhaustion atrophy sets in and permanent cure results. The intensity and duration of therapy depends on which of these

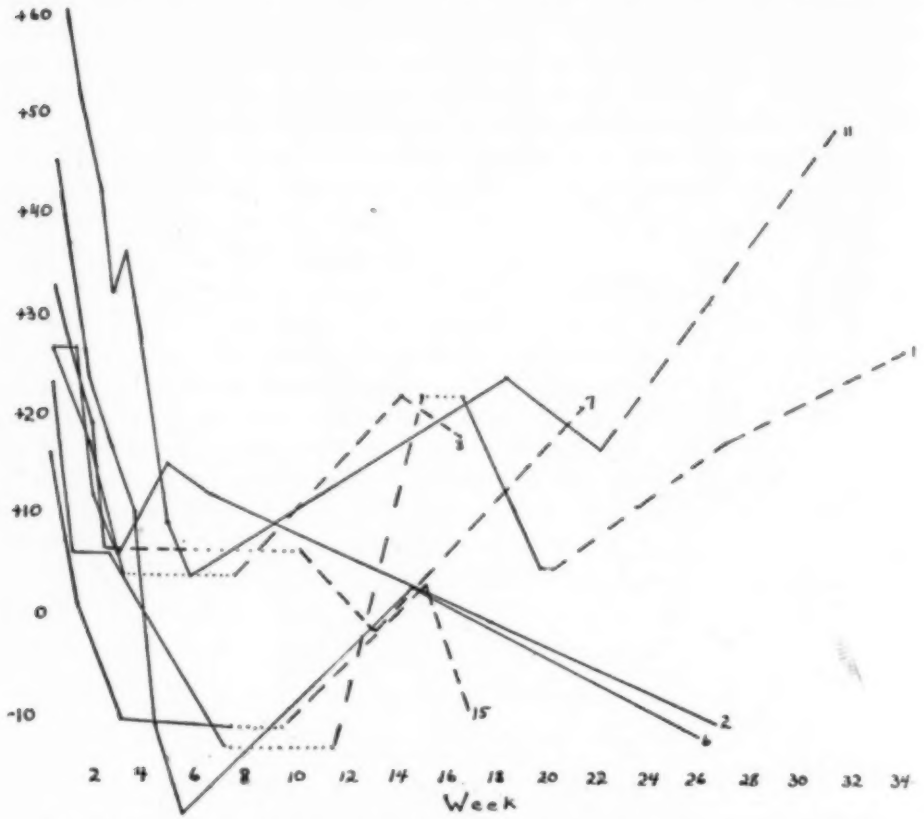

FIG. 2. The effect of prolonged and intermittent thiouracil treatment on the BMR in seven cases. The numbers refer to the cases (see text). The interrupted lines indicate when the patient was not receiving the drug. The dotted lines indicate the time from the last BMR while the patient was receiving thiouracil until the time of cessation of thiouracil administration, no BMR being performed during this period.

ends one seeks. The latter would probably require far more therapy than the former. Unfortunately, however, we have no method of determining when a spontaneous remission would occur or whether thiouracil has induced such a remission. Finally, we have no idea as yet as to how long a period of therapy is necessary for exhaustion atrophy to set in.

That a state of "normality" can be obtained for prolonged periods is illustrated by many of our cases. In case 1, thiouracil was discontinued after two and one-half months of therapy. Nineteen days later the basal meta-

bolic rate had risen, she had lost weight and had noted a recurrence of her symptoms. On readministration of the drug, the basal metabolic rate promptly fell. The drug was stopped a second time. Six weeks later the basal metabolic rate had risen again, but her symptoms did not recur until 16 weeks after cessation of therapy.

In case 11, thiouracil therapy was stopped after 22 weeks. Nine weeks later, the basal metabolic rate had risen markedly. Many weeks later, however, she still continued asymptomatic.

In case 8, thiouracil was administered for eight weeks and then stopped. Six weeks later the basal metabolic rate had risen, but the symptoms had not recurred.

Case 10 received thiouracil for three and one-half months, and then it was stopped. Three months later, the basal metabolic rate had risen, but the symptoms did not return until five months had elapsed.

A very mild case of Graves' disease, case 15, received thiouracil for eight weeks. The drug was then stopped for a period of seven months. During this period of time she remained asymptomatic.

Astwood has reported nine cases with prolonged remission, the minimal period of treatment being six and one-half months. He has, however, noted recurrences after a treatment period of 151 days.

We shall now consider the other groups to see what effectiveness was exhibited by thiouracil therapy in spite of any untoward effects that may have occurred.

In the one instance of leukopenia, case 25, Lugol's solution had been administered for four months prior to entrance to the hospital. After two weeks of treatment with thiouracil, the basal metabolic rate had fallen slightly, the pulse had slowed, and she had gained weight. Because of a mild leukopenia, it was deemed advisable to discontinue the drug.

In the patients with drug fever, the period of study was too short to determine the response to therapy, inasmuch as fever occurred within 12 days.

The cases in group C, illustrating a lack of response, are four in number. Case 36 received thiouracil for 30 days during which time he gained weight and the pulse rate was reduced, but the basal metabolic rate remained elevated. Case 37 was treated for 19 days. The basal metabolic rate, pulse rate, and weight remained stationary. Case 38 received Lugol's solution prior to admission to the hospital. She was treated with thiouracil for 20 days with a resultant slight increase in the basal metabolic rate, slight weight loss, and no change in pulse rate. (This transitory rise in basal metabolic rate observed when thiouracil is administered directly after iodine has been employed has been noted by others.) These cases were treated early in our experience, and we now feel that the period of therapy was too short. The last in group C, case 39, was a 51 year old woman with recurrent hyperthyroidism. She had severe diabetes mellitus and auricular fibrillation. After four weeks of thiouracil therapy, the basal metabolic rate fell from plus 40 to plus 16 per cent, and she gained weight. The diabetic status, how-

ever, did not improve. After a period of seven and one-half weeks of therapy she developed leukopenia with a white count as low as 1,400 with 48 per cent polymorphonuclear leukocytes. The drug was stopped for 11 days and then resumed with 0.2 gram instead of the previously employed 1 gram a day. This dosage was evidently not sufficient, and the basal metabolic rate rose to plus 52 per cent, and she again started to lose weight. The diabetes remained severe. The white count rose, but still remained low, and it was not deemed advisable to employ a larger dosage of thiouracil. After three months of therapy, her clinical progress remained unsatisfactory. She was then given Lugol's solution and operated upon.

The expected improvement of diabetes with correction of the hyperthyroidism has been reported by Astwood,[19, 22] and by Palmer,[21] but was not observed by McGavack et al.[48]

Group D includes three cases of hyperthyroidism successfully prepared for operation with the aid of thiouracil. Case 49 exhibited a marked response in the basal metabolic rate in two weeks, plus a gain in weight and a fall in pulse rate. She was operated upon successfully after 18 days of preparation. Case 42 showed a slow response. After four weeks the basal metabolic rate had fallen from plus 48 to plus 30 per cent, and the pulse remained rapid. He had, however, gained weight and felt subjectively improved. Operation was successfully performed.

CHART II

Blood Cholesterol Determinations before and after Thiouracil Therapy

Before	Case	After
180	5	360
180	6	360
260	2	310
150	3	230
200	14	400
170	16	160
290	21	300
180	23	340
140	4	280

Group E consists of three cases of non-toxic goiter. In cases 45 and 43 the administration of thiouracil for four and one-half and five weeks, respectively, was without effect on the basal metabolic rate, pulse rate, and weight. Also in a third case of non-toxic goiter with some features of a questionable mild hyperthyroidism, no effect was noted after four weeks of therapy.

The Effect of Thiouracil on the Blood Cholesterol. The level of the blood cholesterol has never been a very good index of the degree of hyperthyroidism. Our data are still relatively incomplete. The data available show a rise in the blood cholesterol level in seven instances and no change in two, concomitant with clinical improvement (chart 2).

The Effect of Therapy on Renal Function. In none of our cases have we noted any adverse effects on renal function as determined by routine urinary

examination and by the urine concentration test. Palmer [21] noted one case of hematuria.

Effect of Thiouracil on Liver Function. Although Shorr [33] and Paschkis et al.[24] each noted the onset of jaundice in one case, we have noted no impairment of liver function as the result of thiouracil therapy as measured by the presence of clinical jaundice, blood icterus index, cephalin flocculation test, urinary bile, and urobilinogen, and the galactose tolerance test.

Effect of Thiouracil on the Heart. We noted no evidence of cardiac damage as the result of thiouracil therapy. Neither case with auricular fibrillation (cases 24 and 39) returned to normal rhythm. Others have reported both a return to normal rhythm and a failure to return to normal rhythm.

Effects of Thiouracil on the Blood Constituents. No adverse effects were noted on the hemoglobin or red blood cell count. The effects on the white count and sternal marrow will be detailed below.

Effect of Therapy on Exophthalmos. Exophthalmometric readings were performed on our patients, but we are not as yet ready to commit ourselves to any definite comment. We have, however, seen no "malignant exophthalmos" follow thiouracil therapy, as did Williams and Bissell.[29] It has been our impression that there occurs no recession in the exophthalmos.

Effect of Thiouracil on the Size of the Thyroid. It is difficult to measure accurately the size of the thyroid gland. We have seen enlargement of the gland in several patients, especially those in the early stages of the illness, in whom the gland was large to begin with. Recession in size, however, seemed to ensue later. In other patients, we have noted no increase in size, but rather a decrease of varying extent. The glands appear to become somewhat softer, but this, too, is difficult to judge.

The Effect of Iodine on the Thiouracil Treated Patient. We have mentioned earlier that iodine used prior to thiouracil may result in a delay in the therapeutic result. At times there actually occurs an early increase in the basal metabolic rate. This lag is probably due to the storage of colloid by the thyroid gland while iodine is being administered. A longer period is, therefore, required before the colloid can be utilized and the effect of thiouracil can be noted.

We have had no experience in the simultaneous use of iodine and thiouracil. Mackenzie and Mackenzie [16] thought that iodides potentiated the effects of the sulfonamides. Rawson et al.[28] made comment on the glands of some patients treated with both, but no comment was made as to the clinical effect. Astwood [47] found that iodine resulted in a further fall in the basal metabolic rate, and believed that it caused storage of thyroid hormone in the gland. Williams [29] felt that no effect other than that of the thiouracil could be noted.

In two instances in which iodine was used after thiouracil was discontinued, Williams [29] noted a slight increase in the basal metabolic rate. Our experience in this regard is based on the use of iodine in preparation for opera-

tion in four cases of drug fever due to thiouracil, one case of leukopenia,[25] and case 39. In all instances iodine therapy was started after thiouracil had been discontinued.

Case 34 received 0.6 gram of thiouracil daily for 11 days, and then developed fever. Three days later he was given 0.2 gram and exhibited a recurrence of fever. Four days after this, he was given Lugol's solution, which he received for 12 days and was then operated upon. The basal metabolic rate before treatment was plus 44 per cent, after thiouracil plus 32 per cent, after iodine plus 25 per cent. With iodine therapy he gained seven pounds in weight and the pulse rate remained slow, as it had always been. He died two days postoperatively of a massive pneumonia, confirmed by postmortem examination. The postoperative clinical picture was not that of true storm, and at autopsy an extensive pneumonic consolidation of the right lower lobe was found.

Case 33 received thiouracil for 10 days, at which time he developed a rise in temperature to 103° F. Lugol's solution was started six days later and administered for 21 days. The basal metabolic rate before treatment was plus 41 per cent. It did not fall on thiouracil therapy, but fell after the administration of iodine without any intervening rise, to plus 22 per cent. He was operated upon successfully.

Case 35 received thiouracil for 10 days when there occurred an elevation in temperature. The drug was discontinued, but one dose of 0.2 gram was given three days later, directly followed by another episode of fever. Ten days later, Lugol's solution was administered and continued for 11 days. The basal metabolic rate before therapy was plus 23 per cent. It fell to plus 13 per cent after thiouracil. Further basal metabolism determinations were not performed but because of a gain in weight and a slowing of the pulse operation was performed and was not followed by any untoward results.

Case 32 had a basal metabolic rate of plus 47 per cent before therapy. She received thiouracil for eight days, and 0.2 gram one week later. The basal metabolic rate remained elevated. Ten days later she was given Lugol's solution. After seven days on iodine therapy the basal metabolic rate was minus 7 per cent.

Case 25 received iodine before entrance to the hospital. Thiouracil was given for 16 days and then after one day of delay Lugol's solution was administered for 10 days. The basal metabolic rate fell from plus 34 to plus 23 per cent on thiouracil. On iodine the basal metabolic rate fell to plus 20 per cent. The operation and postoperative course were uneventful.

Case 39 was on thiouracil for 65 days with only slight interruption. Lugol's solution was then administered over a period of one month. The basal metabolic rate fell from plus 52 per cent to plus 26, plus 18, plus 23, and finally to plus 19 per cent. The patient was successfully operated upon and made an uneventful recovery.

It is difficult to decide when the thiouracil effect wears off and when the iodine effect begins, and until there is accumulated a larger collection of data

with varying periods of thiouracil therapy and iodine administration, we shall not have the answers to our problems. But our data would seem to indicate that the use of iodine, following the cessation of thiouracil therapy, did not result in any untoward effects.

The Toxic Effects of Thiouracil Therapy. The toxic effects that we have encountered are tabulated in chart 3.

CHART III

Toxic Manifestations of Thiouracil

A. Indications for further therapy:
   1. Conjunctivitis—5 cases
   2. Edema—1 case
   3. Variegated complaints
      Dizziness
      Aches and pains
      Burning in throat

B. Contraindications for further therapy:
   1. Drug fever with rash—2 cases
   2. Drug fever without rash—2 cases
   3. Agranulocytosis—6 cases
   4. Leukopenia—3 cases

Conjunctivitis. There were five cases of conjunctivitis. One occurred during the first week of therapy, and three occurred during the second and third weeks. All were mild and transient, in spite of the fact that the drug was continued. One occurred after two and one-half months of treatment, was rather intense and persisted for several weeks, but disappeared during further treatment with thiouracil.

Edema. One case of frank diffuse edema occurred after five weeks of treatment. No cause other than the thiouracil therapy could be established as the underlying factor. The urine and kidney function tests were negative. The total proteins of the blood were 6.0 grams per cent. The albumin fraction was 4.5, and the globulin fraction was 1.5 grams per cent. The serum sodium was 138.6 milliequivalents per liter, and chlorides 108.0. The basal metabolic rate was plus 1 per cent. The edema receded spontaneously and did not recur with further therapy. Other instances of edema have been reported by Williams et al.[38] who studied these cases intensively, and by Palmer.[21]

Slight transient puffiness of the eyes was complained of by several other patients.

Variegated Complaints. There were rather frequent complaints of dizziness and aches and pains in the joints that had not been present before treatment with thiouracil was begun. Whether these were simply psychoneurotic in origin or related to the drug administration we cannot say. Others complained of burning in the throat after ingestion of the drug. In a few, transient skin eruptions were noted that disappeared in spite of the continuation of treatment. Other observers have noted similar rashes.

Drug Fever. There were four instances of drug fever, including two previously reported by Gabrilove and Kert.[32] Two of these were accom-

panied by a generalized maculopapular rash, and one of these latter had a generalized lymphadenopathy. In three of these patients a single subsequent dose of 0.2 gram of thiouracil provoked a recurrence of the fever and thereby proved the drug origin of the pyrexia. The fever began on the eighth, tenth, tenth, and eleventh day after thiouracil therapy was instituted.

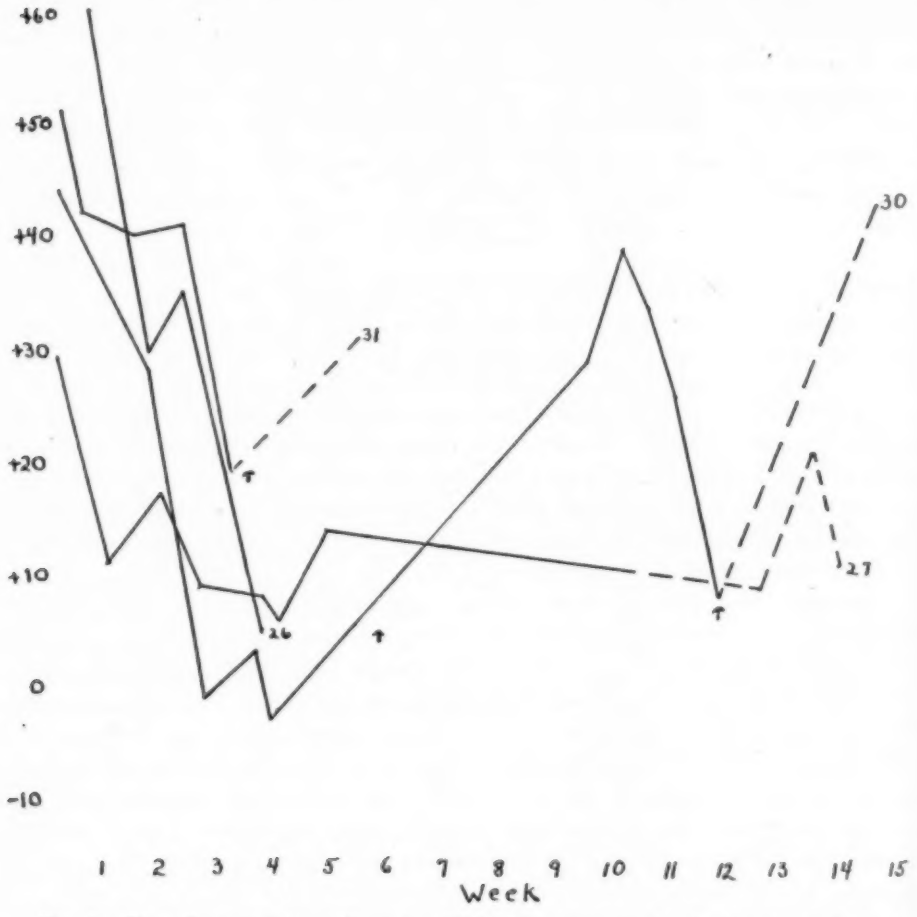

FIG. 3. The effect of thiouracil on the BMR in four cases developing agranulocytosis. The arrows indicate the onset of agranulocytosis. The interrupted lines indicate the time during which the patient was not receiving the drug.

Agranulocytosis. The most dangerous, and unfortunately comparatively frequent, complication of thiouracil therapy is agranulocytosis (granulocytopenia). We have encountered six cases of agranulocytosis in cases of hyperthyroidism treated with thiouracil.

The first case in our experience was that of a 47 year old woman with hyperthyroidism, who had an excellent response to thiouracil (case 26, figure 3). She was discharged from the hospital markedly improved. At the end of four and one-half weeks of therapy of 1 gram a day her white blood

count was 5,800, with a normal differential. She was discharged from the hospital for follow-up study in the clinic. She was readmitted 12 days later. Three days prior to her readmission, she noted fever, chills, a congested nose and throat, cough and dysphagia. The thiouracil which she had been taking in daily doses of 0.4 gram was discontinued. A blood smear taken at this time, but examined only at the time of readmission, revealed six segmented polymorphonuclear leukocytes, two non-segmented polymorphonuclear leukocytes, 90 lymphocytes and two monocytes. On admission, the hemoglobin

CHART IV
(Case 29)

Detailed Blood and Sternal Marrow Studies on a Patient Who Developed Agranulocytosis with Thiouracil Therapy

Day of Admission	−21	−1	0	1	2	3	5	6	7	11	14	20
Hemoglobin	100	86	80	85	72	80		105	117	111	101	
R.B.C.	4.76	4.62		4.65						5.54		
Platelets				300				210				
W.B.C.	7,500	3,250	2,240	1,250	1,400	1,700	4,100	5,100	7,250	114,000	138,000	7,650
Myelocytes								5				
Non-Seg. Neutrophiles	10	2		3	2		7	9	6	6	10	
Seg. Neutrophiles	55	1				1	4	28	50	52	64	68
Lymphocytes	33	97	98	95	98	96	84	48	35	38	18	26
Monocytes	2		2			3	2	9	9	4	6	5
Basophile				1							1	1
Eosinophile								1			1	
Plasma				1								
Sternal Marrow Puncture												
Nucleated Count				15,000	120,000			110,000				
Megakaryocyte				0	11			44				
Myeloblast				5.0	2.0			2.0				
N. Myelocyte				9.0	11.0			45.2				
E. Myelocyte				0	0.5			0.4				
B. Myelocyte				0	0.5			0				
Non-Seg. Neutrophiles				2.0	0			17.2				
Seg. Neutrophiles				0	0			2.4				
Lymphocyte				32.0	13.5			7.2				
Hematogone				16.0	12.0			7.8				
Plasma Cell				3.0	4.5			0.8				
Reticulum Cell				7.0	3.0			0				
Monocyte				1.0	0			0				
Megaloblast				1.0	0.5			0				
Erythroblast				2.0	2.0			0.8				
Normoblast				21.0	43.5			18.0				

was 87 per cent, the red blood count 4.53 million, white count 200 with 100 per cent lymphocytes. The platelets were 120,000. Sternal marrow aspiration revealed 11,000 nucleated cells with a differential of 8 per cent myeloblasts, 20 per cent lymphocytes, 10 per cent hematogones, 10 per cent plasma cells, 20 per cent reticulum cells, 30 per cent normoblasts, and 2 per cent megakaryocytes. In spite of treatment with intravenous sulfamerazine and blood transfusions, she died on the third hospital day. Just prior to her death, the white count was 800 cells per cu. mm. with 100 per cent lymphocytes. The blood culture was sterile.

The remaining five cases in our series all survived. We attribute these good results to the generous use of penicillin and blood transfusions. This therapy served to control infection and enabled the patients to survive until such time as granulocyte formation was again normally resumed.

The second case in our series was a 50 year old woman treated by her private physician for hyperthyroidism with thiouracil. She had responded well to 0.5 gram a day for seven weeks. One day prior to admission she noted fever, sore throat and headache. A white blood cell count was 3,250 per cu. mm., of which 97 per cent were lymphocytes and one was a polymorphonuclear leukocyte. The next day the total white count had fallen to 2,240, and the day after to 1,250 per cu. mm. with a total absence of granulocytes. Chart 4 summarizes the blood findings in this case. She was treated with penicillin and blood transfusions. Her temperature remained elevated for five days and then began to return to normal levels. Concomitantly there occurred a progressive improvement in the peripheral blood and bone marrow.

CHART V

(Case 27)

Blood and Sternal Marrow Studies in a Patient with Agranulocytosis

Day of Admission	−9	0	1	2	3	4	5	6	7	11	16
Hemoglobin	75		76	86		86				105	
Red Count	4.2		4.19			4.75				5.45	
Platelets				300		310					
White Count	5,100	1,200	600	950	2,350	2,400		5,400	5,850	11,300	7,650
Myelocytes	8				2		6	1	3	2	
Non-Seg. Neutrophiles		6	8	10	18	12	23	27	15	14	6
Seg. Neutrophiles	60	2	6	2	29	14	10	28	37	41	54
Lymphocyte	34	90	84	48	36	62	50	37	38	34	32
Monocyte	5	2	2	28	10	6	8	4	2	5	7
Basophile				2	1						1
Eosinophile	1			2	1	2	2	2		2	
Plasma					3		1	1	5	2	
				Sternal Marrow Studies							
Nucleated Count			70	105							475
Megakaryocyte			88	132							110
Myeloblasts			4.0	3.6							0.2
N. Myelocytes			34.0	61.6							32.3
E. Myelocytes			2.0	0							0.3
Non-Seg. Neutrophiles			0	0							40.0
Seg. Neutrophiles			0	0							6.6
Eosinophiles			2.8	0.4							0.6
Lymphocytes			20.4	7.6							3.3
Hematogone			7.6	9.2							3.3
Reticulum			1.2	0.8							0.3
Plasma			1.6	1.2							0
Megakaryocyte			0.4	0.4							0
Megaloblast			0	0							0.3
Erythroblast			0	0.4							0.7
Normoblast			25.6	14.8							8.3

The third case, case 27, was that of a 43 year old woman with hyperthyroidism. She was treated with thiouracil with dosages of one gram a day for 32 days and then 0.2 gram for 34 days. She had been hospitalized for the first 37 days of the therapy, and then was seen in the clinic weekly. Nine days prior to admission she had had a blood count, which was entirely normal. Five days prior to admission, she developed fever, cough, sore throat, a "stuffed" nose, and headache, and she stopped taking thiouracil. She was sent into the hospital, where the white blood cell count was found to be 1,200 per cu. mm., of which only 8 per cent were of the granulocytic series. The next day, the count had fallen to 600, although 14 per cent were

now polymorphonuclear leukocytes. She was treated with penicillin, blood transfusions, and liver extracts, and responded very well. The febrile course lasted four days. Her hematological picture is illustrated in chart 5.

The fourth case was that of a 58 year old man with hyperthyroidism, who was treated with 0.6 gram of thiouracil for 22 days, and then 0.2 gram for 44 days. While under observation in the hospital, he developed agranulocytosis. The white blood cell count fell to 1,600 per cu. mm., of which 2 per cent belonged to the granulocytic series. The changes in his marrow and peripheral blood are illustrated in charts 6 and 7. He was treated with penicillin, pentnucleotide, and blood transfusions. He was febrile for six days, but did well thereafter (case 30).

CHART VI

(Case 30)

Peripheral Blood Studies in a Patient with Agranulocytosis

Date	Hemoglobin	R.B.C.	W.B.C.	Seg. Neut.	Non-Seg. Neut.	Lymphocyte	Monocyte	Eosinophile
4/15			8,500	61	4	24	8	3
6/20	82	4.38	6,300	45	2	44	3	3
6/23			4,000	54	5	36	2	3
6/27			3,700	53	2	44	1	
7/3			2,200	21	5	72		2
7/6			1,900	3	4	92		1
7/7			1,600	2	1	97		
7/8	72		1,900	1		99		
7/10			1,900	1		99		
7/11			1,600	1		97	1	1
7/12	68		1,900	1		99		
7/13			2,000	1		99		
7/14			1,900	2	2	96		
7/15			2,100	2		94	4	
7/17			3,000	20	6	72	2	
7/18			3,500	14	5	78	3	
7/20			4,200	3	10	60		
7/22			4,000					
7/25	90		7,000	33	2	60	15	

CHART VII

(Case 30)

Sternal Marrow Studies

	7/8	7/13
Nucleated Count	96,000	80,000
Megakaryocyte	22	44
Myeloblasts	2.0	5.2
Promyelocytes	0.4	0
N. Myelocyte	0	36.0
E. Myelocyte	0.8	1.2
Non-Seg. Neutrophiles	0.8	0.8
Eosinophile	0.4	0.4
Lymphocyte	3.0	7.2
Hematogone	58.8	7.6
Plasma	0	0.8
Reticulum	0	0.4
Megaloblast	0	0.4
Erythroblast	5.6	1.6
Normoblast	28.8	38.4

The fifth case, that of a 53 year old man with hyperthyroidism (case 31), also afforded us the opportunity to study the development of agranulocytosis while the patient was hospitalized. He was treated with 0.6 gram a day for 25 days when he developed sore throat and fever. A white blood cell count at this time showed the presence of only 950 cells per cu. mm., of which 10 per cent belonged to the granulocytic series. The next day, although the total white count had increased to 1,575 per cu. mm., the granulocytes had entirely disappeared from the peripheral blood. The changes in the peripheral blood and sternal marrow are illustrated in charts 8 and 9. He was treated with penicillin and blood transfusions, was febrile for 10 days, and then recovered completely.

The sixth case (case 28), the details of which were furnished by Dr. N. Rosenthal, who treated this patient in the Private Pavilion of The Mount Sinai Hospital, was a 29 year old woman with hyperthyroidism, who had received 0.6 gram of thiouracil a day for 35 days. Blood counts were not done. Five days prior to entrance into the hospital, she noted fever and painful gums. She was seen by her physician and by her dentist, and was then referred to Dr. Rosenthal. On the third day of this patient's hospital admission, the total white blood cell count had fallen to 600 per cu. mm., with only one basophile in the peripheral blood, representing the granulocytic series. She was treated with liver extract, penicillin, and blood transfusions, and did well, being febrile for only five days. Her hematological picture is illustrated in charts 10 and 11.

The time of occurrence of the agranulocytosis in these cases was 40, 49, 66, 80, 25, and 35 days after onset of therapy. The total dosages employed were 15.0, 21.0, 24.5, 27.6, 34.6, and 49.0 grams.

We do not believe that these toxic reactions are due to a direct depression of the marrow by an overdosage of drug, but rather that it represents a curious sensitivity on the part of the patient, similar to that observed with other drugs with a similar organic nucleus.

These hematological complications will be reported in greater detail by Drs. Vogel, Tyson, and Rosenthal.

We wish to call attention to our results in the treatment of agranulocytosis with penicillin and blood transfusions. Of the six patients with this unfortunate complication, one died and the remaining five recovered. This fatality occurred prior to our use of chemotherapy in these cases. In the remaining five patients, penicillin was administered in a dosage of 20,000 units intramuscularly every three hours day and night, and small blood transfusions were given daily. Since the primary cause of death in the patients with agranulocytosis is overwhelming infection, the rationale for the use of penicillin is postulated on the attempt to control such infection until such time as the normal formation of granulocytes is resumed.

Anatomical Changes in the Thyroid Gland Following the Use of Thiouracil. From animal experimentation with thiouracil detailed previously

CHART VIII

(Case 31)

Peripheral Blood Studies in a Patient with Agranulocytosis

Date	Hemoglobin	R.B.C.	Platelet (thousand)	W.B.C.	Segmented Polymorphonuclear Leukocyte	Non-Segmented Polymorphonuclear Leukocyte	Lymphocyte	Monocyte	Eosinophile	Plasma	Macrophage
7/13	83	4.52		8,550	57	6	33	4			
7/24	75			5,450	45	2	47	3	3		
7/26	79			6,000	43	5	40	6	6		
7/28	78			3,600	40	7	45	1	3		
7/31	81			4,800	48	7	35	8	2		
8/4	80			3,700	37	3	57	1	2		
8/7	70			3,550	43	8	47	1	1		
8/9	79			4,800	40	10	47	4		2	
8/11	68			950	6	3	88	2	1		
8/12	69	4.1	300	1,575			98	2			
8/13				1,000			80	20			
8/14	85			1,450			98	2			
8/15	80	4.4	260	1,400			99	1			
8/16	79	4.5		1,200			99	1			
8/17				1,200			99	1			
8/18	75			1,300			96	2		2	
8/19				1,750		2	94	4			
8/20				2,200	3	1	85	7	4 myelocytes		
8/21				2,650	5	13	77	5			
8/22		5.5	260	3,100	9	18	62	11			
8/23				3,450	13	14	68	5			
8/24	107			2,750	13	10	66	10			
8/25	102			4,500	22	11	53	13			1
8/26				4,050	55	8	28	9			

CHART IX

(Case 31)

Sternal Marrow

Date	8/11	8/16	8/22
Nucleated Count	50,000	45,000	175,000
Megakaryocytes	66	44	44
Myeloblasts	2.0		2.0
Promyelocytes		0.5	12.7
Myelocytes, Neutrophile			55.0
Myelocytes, Eosinophiles			0.7
Non-Segmented Neutrophiles			10.0
Segmented Neutrophiles	0.4		1.0
Lymphocyte	17.6	3.5	2.0
Hematogone	6.8	7.0	2.3
Plasma	2.0	5.5	3.0
Reticulum	0.8	2.0	1.0
Myeloblast	0.4	0.5	
Erythroblast	0.8	4.5	0.3
Monoblast	69.2	76.0	10.0
Megakaryocyte		0.5	

we have learned what the anatomical changes are that occur in the thyroid glands. These changes are diffuse hyperplasia and hypertrophy of the gland, lymphoid infiltration, and increased vascularity. However, changes in the human being treated with thiouracil may not occur to the same degree as in animals, for several reasons. Evaluation of treatment in a patient with hyperthyroidism is often very difficult, for one must take into account the length of time the disease has existed, the previous use of iodine and radiotherapy, the natural history of remission and relapse, and the varying degrees of severity. The thyroid gland may reflect in its histology all of these factors, so that even the gland from an untreated patient may show various types of change, varying from marked hyperplasia to marked involution. The knowledge that the human thyroid may go through a cycle of hyperplasia and involution (Marine cycle) must be borne in mind. The thyroid glands of experimental animals are "biologically young" and easily susceptible to external influence, but in man, the thyroid gland, having passed through varying numbers of cycles, depending on the stage of the disease, may be resistant to induced change. There may be several adenomata and foci of nonresponsive thyroid tissue present. Patients in the early stages of thyrotoxicosis with diffuse hyperplasia are probably the patients whose thyroid glands are most satisfactory for study. There are many other factors which influence the appearance of the gland after thiouracil treatment. For example, patients with hyperthyroidism have hyperplasia and hypertrophy as part of the picture of the underlying disease. It is, therefore, difficult to decide how much is due to the disease and how much is due to the drug, unless a biopsy had been taken before the administration of the drug.

The period of treatment with thiouracil is relatively short, and the dosage is relatively small compared to the dosage employed in animal experimentation. The changes, therefore, may not be so striking in the human gland.

Finally, patients with normal thyroids or colloid goiter may have a large store of colloid and thyroid hormone. It will, therefore, take a considerable time to deplete these stores and consequently a longer period of time for the clinical effects of the drug to be noted and the anatomical effects to occur. We presume that the hyperplasia results from the low levels of circulating thyroid hormone with a resultant stimulation of thyrotropic hormone secretion and not as the result of the prevention of manufacture of thyroid hormone per se.

Other factors, such as the use of iodine before, during, or after thiouracil, alter the histological picture and make any interpretation difficult. Only by collecting a large number of cases, changing one variable at a time, will we be able to weave the entire picture.

The glands that we have available for study are: (A) one case in which death resulted from agranulocytosis (case 26) and three cases of hyperthyroidism prepared for operation with thiouracil (cases 40, 41, 42), all of these cases representing the action of thiouracil in hyperthyroidism; (B) three cases of non-toxic goiter treated with thiouracil preoperatively to note

the effect of the drug; (C) eight cases of hyperthyroidism prepared with thiouracil for varying periods of time and followed by the use of iodine for a minimum of two weeks.

In case 26, there were seen the most characteristic hypertrophy and hyperplasia. The thyroid gland was diffusely enlarged. The history of hyperthyroidism had been of two years' duration; thiouracil had been employed for about six weeks.

In case 40, the gland clinically was diffusely enlarged. The symptoms were of eight months' duration, and thiouracil had been employed for 18 days. In this gland, too, there was considerable hypertrophy and hyperplasia. A few small acini were seen filled with colloid.

In case 41, the histological picture was that of a micro- and macro-follicular adenoma.

In the group of non-toxic goiter, there was one gland which exhibited marked hyperplasia and tremendous amounts of lymphoid tissue. Whether the latter bears any relation to the thiouracil therapy or whether it was present before treatment, we cannot say. Such collection of lymphoid tissue has been reported by others.

The other two glands revealed colloid adenomata, one with a papillomatous area, the other with the trabecular adenoma.

Of the other cases studied, which have received thiouracil followed by iodine (cases 30, 34, 33, 35, 25, 38, 39, 37), one case (34) showed tremendous hyperplasia and hypertrophy. Six showed a histological appearance similar to that seen in Graves' disease in a colloid phase, two being rather hyperplastic. One showed the structure of a micro- and macro-follicular adenoma, but the gland clinically was rather nodular (case 35).

Summary

1. Thiouracil has been used in the treatment of 54 patients. Fifty-one patients of this group had hyperthyroidism, and three were instances of non-toxic goiter.

2. Thirty-three of these patients have been treated successfully with thiouracil for varying periods of time, the longest period of continuous therapy being 10 months. Four of these patients had recurrent hyperthyroidism, the remainder of the patients had diffuse hyperplasia or toxic nodular goiter.

3. Three patients with hyperthyroidism were successfully prepared for operation with thiouracil.

4. Four patients with hyperthyroidism failed to respond satisfactorily to thiouracil. These patients were subsequently prepared with iodine and successfully operated upon.

5. In 11 instances, thiouracil therapy was discontinued because of severe toxic reactions.

6. The following toxic reactions were encountered: conjunctivitis, five cases (9 per cent); edema, one case (2 per cent); drug fever, four cases (7 per cent); leukopenia, one case (2 per cent); agranulocytosis, six cases (11 per cent). Some sort of toxic reaction was encountered in 31 per cent. One of the patients with agranulocytosis died (2 per cent).

7. The development of agranulocytosis or drug fever are indications for cessation of therapy. Treatment may be safely continued in the presence of conjunctivitis.

8. Liver and kidney function studies throughout the course of treatment failed to demonstrate any evidence of injury to these organs resulting from the thiouracil. However, instances of toxic hepatitis occurring during thiouracil therapy have been reported.

9. Because of the frequency and severity of the toxic reactions it is our feeling that thiouracil should be used under the following circumstances:

(*a*) In the preparation of iodine-fast patients for operation.

(*b*) In older individuals with hyperthyroidism, in whom for one reason or another operation is fraught with great hazard.

(*c*) In patients with recurrent hyperthyroidism who have been operated upon twice or more.

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WERNER'S SYNDROME (PROGERIA OF THE ADULT) AND ROTHMUND'S SYNDROME: TWO TYPES OF CLOSELY RELATED HEREDOFAMILIAL ATROPHIC DERMATOSES WITH JUVENILE CATARACTS AND ENDOCRINE FEATURES; A CRITICAL STUDY WITH FIVE NEW CASES *

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OBSERVATIONS on these rare and apparently heredofamilial disorders are scattered throughout the different branches of medical literature according to the particular interest of the individual author specializing in involvement of the eye or the skin or the nervous system.

B. S. Oppenheimer and V. S. Kugel (1934) have the distinction of first reporting this condition in American medical literature, renaming it "Werner's syndrome." The characteristics of this syndrome are:

Shortness of stature, characteristic habitus
Canities (i.e., premature graying of the hair)
Premature baldness
Scleropoikiloderma
Trophic ulcers of the legs
Juvenile cataracts
Hypogonadism
Tendency to diabetes
Calcification of the blood vessels
Osteoporosis
Metastatic calcifications
Tendency to occur in brothers and sisters

The cases published in the literature under different titles have been purposely selected and grouped. It seems necessary to quote and discuss in detail the pertinent literature in order to prove the actual existence of Werner's as well as Rothmund's syndrome and to justify their separation. Observations of our own cases should show that the classification of the skin changes as "scleroderma" or "scleropoikiloderma" is not appropriate, since we are dealing with heredofamilial dermatoses of a special nature. The pathogenesis of the ulcers occurring in Werner's syndrome, either "trophic" or due to "pressure," will be discussed. In addition the relationship of the syndrome under discussion to other clinical syndromes will be demonstrated.

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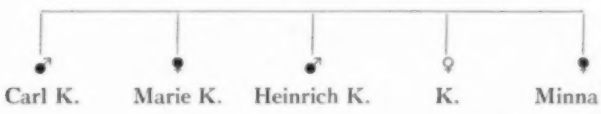
I. Werner's syndrome (progeria of the adult)
II. Rothmund's syndrome
III. Cases related to Werner's syndrome (progeria of the adult) and Rothmund's syndrome
  A. Cataracta dermatogenes (neurodermitis) Type Andogsky
  B. Progeria of children (Hutchinson-Gilford's syndrome)
  C. Myotonic dystrophy
  D. Hereditary ectodermal dysplasia of the hydrotic type. Dystrophy of the hair and nails (Type McKay-Davidson)

I. Werner's Syndrome (Progeria of the Adult)

In 1904 Otto Werner [1] described in his Doctor's thesis from Ophthalmological Clinic in Kiel, a peculiar disorder, under the title "Cataract in Connection with Scleroderma," occurring in four brothers and sisters, two males 40 years and 36 years old, and two females, 38 years and 36 years old (a fifth sister, 33 years old, was healthy).

Family K



The grandfather and grandmother and parents of the patients lived to an old age. There were no interfamilial marriages and no blood relationship. It was only reported that a cousin of the patients, on the mother's side, already showed graying of the hair at the age of 20.

Case Reports

Case 1. Carl K., 40 years old. Normal birth. Normal development in childhood. Short in *stature*. No measures of height were reported. The *appearance* was atrophic and senile. *Hairs* started to turn gray at 20. At 40 they were snow white and very scarce. Nothing is reported concerning eyebrows, eyelashes or pubic hair at the age of 20. *Areas of hyperkeratosis* were first noted under the large toe, under the fifth toe and on the heels. After removal they recurred in a short time. At the age of 40 hyperkeratotic areas were noted over the malleoli, heels, on almost all toes, especially the end phalanx of the left second toe, which was covered with a cap of horny tissue. The *skin* over the lower extremities and on both feet became thickened at 30. *Ulcers* appeared at this time, first on the left third toe and on the skin of the dorsal surface of both feet. The ulcers were as large as a dime. Later ulcers developed on the external malleoli and on the skin over both Achilles tendons. In almost all instances areas of inflammation were observed, especially on the dorsum of the feet. These places were so painful that the patient cried like a child. The taut skin was stretched over the underlying structures which were lacking in subcutaneous fat. In some places fine scales covered the shiny, thin skin. The skin changes were only noted on the lower legs and feet. Because of the tightness of the skin motion in the ankle and phalangeal joints of the feet was considerably restricted. There were no hairs in the afflicted skin areas. Unlike his brother this patient did not complain of

pain in his legs. The *muscles* and *subcutaneous fat tissue* on both lower legs were underdeveloped. On the forearms and hands also, muscles as well as subcutaneous fat tissue were atrophic, but to a lesser degree than on the lower legs and feet. The *toe-nails* were lacking on the left third and fourth toes and on the other toes the nails were atrophic. A similar condition of the nails was noted on the right foot. There is no report on the character of the *voice*. *Cataracts* developed at the age of 28 and were operated upon at the age of 36. *Endocrine features:* Other than the senile atrophic appearance there was no report on the sex organs or his sexual life. The fact that he was not married hints at a sexual deficiency.

Case 2. Marie K., 38 years old. Normal development as a child. She was very short in *stature* and gave the general impression of being an underdeveloped, degenerated person, with thin muscles and very little subcutaneous fat tissue. *Hairs* were fine, gray and scarce. *Psyche* and intelligence were normal. *Skin:* At the age of 22 the patient noted that the skin of both lower legs and feet had already become taut and fixed on the underlying structures. The veins under the thin atrophic skin became visible in their smallest ramifications. There were no hairs on the affected parts of the skin. Because of the tightness of the stretched skin motion of the ankle joints and phalangeal joints was almost impossible. The color of the skin was normal, except that the face had a reddish hue due to severe acne. When she was 32 an ulcer developed on the skin covering the left outer malleolus which did not close for two years. When she was 34 an ulcerative skin defect, the size of a walnut, located on the left lower edge of the shin bone, which, after several years, had not yet healed. At the time this 38 year old patient was first seen the skin of both lower legs was taut, glossy and atrophic. The skin on the affected parts showed patches of grayish brown discoloration beside normal skin of normal color. Slight scaling was noted on sharply defined places where the normal skin bordered the affected parts. Areas of thick *hyperkeratosis* were present over both heels, under the large toes, on the lateral sides of the feet and on the dorsum pedis on several toes. Ulcers and scars of ulcers were seen on all parts exposed to pressure on both lower legs. Especially large ones were located over both Achilles tendons, on both shins, on the malleoli and on the lateral sides of the feet and on the back of some toes. On the large toe of the left foot only a rudimentary nail had developed. On all other toes of the left foot nails were lacking. Of special interest was the severe involvement of the skin of both lower arms and hands. The thin, reddish, atrophic skin over both hands was so tightly stretched over the bony structures that the first and second phalangeal joints on all fingers were ankylosed. The patient could not move her fingers. The fifth finger of the left hand was contracted in flexed position. Defined areas of hyperkeratosis similar to the condition on the feet were noted over the metacarpophalangeal and over some interphalangeal joints. The finger-nails were normal except that of the left fifth finger which was atrophic. The muscles of both lower arms were atrophic and meager. The subcutaneous fat tissue was almost lacking on both lower arms and hands. Tendon reflexes were normal. *Cataracts* developed on both lenses at the age of 23. The cataracts matured six years later and were successfully operated upon. *Endocrine features:* The thyroid gland was enlarged to the size of a fist. The patient did not complain of palpitation or other symptoms of hyperthyroidism. Menstruation had started at the age of 13 and had been regular until the age of 20. Thereafter the patient menstruated only twice a year for a few years, then menstruation ceased altogether.

Case 3. Heinrich K., 36 years old. He was a farmer and was able to work until his eyesight deteriorated at the age of 33. As a child his development was normal. No record of his height was reported. At the time of his first examination his *appearance* was senile. After he graduated from high school his *hair* began to turn gray. At the age of 24 all the scalp hair was grayish. There was no report of the

presence or absence of pubic hairs. His bony structure was very thin. The skin was of senile texture and shrivelled. A withered condition was especially noted on the skin of the face. Tightness of the skin in Heinrich K. was observed only on both feet and the lower third of the lower legs. The skin in these areas was taut and atrophic and of a reddish hue. Some areas of the feet were puffy and itching. Slight scaling on some areas was noted. The mobility of ankle and phalangeal joints was not restricted. Only over the olecranon of the right elbow circumscribed areas of *hyperkeratosis* were seen. *Ulcers* were present only on two areas, namely, on the skin over the right malleolus and over the medial side of the large toe. *Cataracts* developed at the age of 29. The patient was operated upon at the age of 33. The arterial *blood vessels* exhibited definite signs of arteriosclerosis. *Endocrine features:* Other than his senile, atrophic appearance no remarks concerning endocrine symptoms were made.

Case 4. Minna K., 31 years old. Her development in childhood was normal. At the time of her examination she gave the impression of a degenerated and infantile person. She was of *very short stature*. Her *psyche* was abnormal. She cried and laughed without reason. She was suspicious and refused at first to be examined. Her scalp *hairs* were entirely gray. The first *skin* changes were observed at the age of 22. The skin over the second and third left toes became thickened and covered these toes like a horny "capsule." After the horny layer was removed an *ulcer* remained. Both toes had to be amputated. Two years later the same condition resulted in the amputation of the fourth left and second right toes. At the time of her examination, at the age of 31, both feet were deformed because of the previous operations. The arches were abnormally high. Exostoses were present on lateral parts as well as on the dorsal parts of the feet. There was slight scaling of the skin over the lower legs and feet and it was taut and atrophic, but of normal color. The skin was so tightly stretched over the bony structures of the feet that the mobility in both ankle joints was almost completely restricted. Numerous telangiectases of the skin covering the malleoli and the exostoses were noted. Areas of *circumscribed hyperkeratosis* were outstanding on both heels and over the exostoses. The nails of the two remaining toes of the left foot had completely disappeared; the end phalanges of these toes were atrophic. The nails of the four remaining toes of the right foot were present only in rudimentary form. The muscles of both lower legs were extremely thin and underdeveloped. The panniculus adiposus in this part of the legs was almost completely absent. Although the bony structures of the whole body were extremely thin and fragile, spontaneous fractures had never occurred. *Cataracts* developed at the age of 27, first on the right eye and, two years later, on the left eye. *Endocrine features:* The thyroid was enlarged forming a goiter the size of an apple. No signs of hyperthyroidism were noted. During her adolescent years the menstruation was rare and scanty. At the age of 19 the menses stopped completely. Her presenile appearance was outstanding.

Comment. There is no question that Werner's observations on four brothers and sisters represent the first description of a unique clinical entity. Werner, a medical student in the ophthalmological ward, was concerned chiefly with the juvenile cataracts, but the description of the appearance of these patients, especially the detailed appearance of the skin changes, at once gives the impression that the described disease is of general medical interest and significance since it involves not only the eyes but the whole body. All the symptoms of these brothers and sisters developed during the second and third decades of life. Birth was normal, development in childhood was

normal, but in the adolescent age they remained short in stature. It is remarkable how similar, almost to the last detail, the other features likewise appeared in these patients. They became gray around the age of 20, later the skin on the lower legs became taut, atrophic and stretched over the underlying tissues, which consisted of a very meager subcutaneous fat tissue and thin atrophic muscles. Areas of circumscribed hyperkeratosis were painful and after the horny layer was torn off or removed by the pressure of shoes or clothes ulcers resulted. At the same time, in the second decade of life, cataracts developed in both eyes. The whole appearance became more and more senile. The patient became incapacitated for heavy work, partly owing to the immobilization of the ankle joints and feet as a result of the tightness of the skin and the ulcers, and partly owing to general weakness and to the reduced nutritional status of the whole body. Signs of arteriosclerosis became evident and completed the picture of presenility.

Werner has classified the skin changes as scleroderma because the skin of these patients in the affected areas was taut and tightly stretched over the underlying tissues, as in true scleroderma. He did not consider that the circumscribed hyperkeratosis and ulcer formation are not observed as features of true scleroderma nor did he make biopsies to prove his classification histologically. Unfortunately this designation, as will be noted, was used in similar familial cases later published. On the basis of our own observations an effort will be made to classify the nature of the skin changes simulating scleroderma in Werner's syndrome. Werner, himself, relates the observations made on the four adult members of the family K. to observations published by Rothmund 61 years ago, describing young people of three different families in whom peculiar skin changes, together with cataracts, occurred. The difference and the relationship of the syndromes described by Rothmund on the one side and by O. Werner on the other will be pointed out in the second part of this paper.

A. Vossius,[2] in 1920, reported two cases with scleroderma and cataract.

Case 1 was a 57 year old, intelligent woman, with a small skull. The scalp ***hair*** was snow white and scarce. Proptosis of the eyes was noted. The *voice* was high pitched and hoarse. *Scleroderma* developed at the age of 20 and bilateral *cataracts* at the age of 31. No similar disorder in the family was reported.

Case 2 was a 35 year old male who was short in *stature*. The muscles and adipose tissue were underdeveloped. The *voice* was high pitched and hoarse. Scleroderma started at 20 and *cataract* at 30. One sister was reported to be of the same small stature as the patient.

G. Guillain, J. T. Alajouanine and R. Marquezy[3] (1923) reported a male patient, 28 years old, under the title "Sclerodermie progressive avec cataracte double précoce chez un infantile."

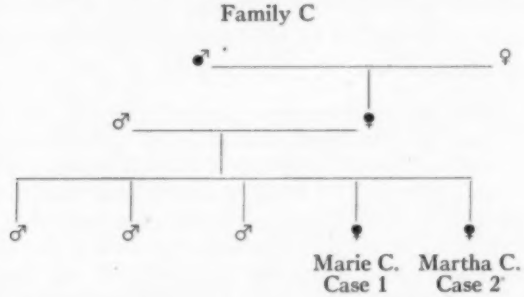
No other members of the family were afflicted. He was short in stature (148 cm.) and his growth stopped at the age of 10. The *extremities* were short and thin in contrast to the chest and abdomen. Hands and feet were small. The fingers showed nodular deformities as in arthritis. *Hair:* Face and chin were hairless with the exception of a few fine mustache hairs. Pubic hairs were scarce and of a female distribution. The skin was tight and not pliable on the lower part of the legs,

especially on the toes. The skin was fine in texture on the dorsum of the feet. Under the great toes, areas of *hyperkeratosis* were found. *Ulcers* were also present under the great toes as well as on points of pressure. The muscles on the lower part of the legs were atrophic. Above the knee the *muscles* were normal. On the face, chin and arms the *skin* was also tight but less so than on the feet. There was some difficulty in opening the mouth wide. No telangiectases were noticed. *Cataracts* developed in both eyes when he was 25. The *voice* was harsh and high pitched. The *heart* was normal. Blood pressure was 140 mm. Hg systolic and 90 mm. diastolic. *Endocrine features:* Gynecomastia of both breasts. Although the genital organs were very small and the testes were only the size of those of a 10 year old boy the patient claimed to have had intercourse three to four times in a single night. He had married at the age of 24 but had no children. Sella turcica was normal. Roentgenograms of the bones showed the epiphyseal fuges closed.

N. Manjukowa,[4] in 1923, in a paper concerning the relation of cataract to endocrine disturbances, described a 36 year old man whose features apparently belong to the syndrome under discussion, whereas a patient, reported in 1922 by *C. Papastratiyakis,*[5] with complete alopecia, atrophy of the nails and cataracts, should not be registered as Werner's syndrome but rather as "hereditary ectodermal dysplasia."

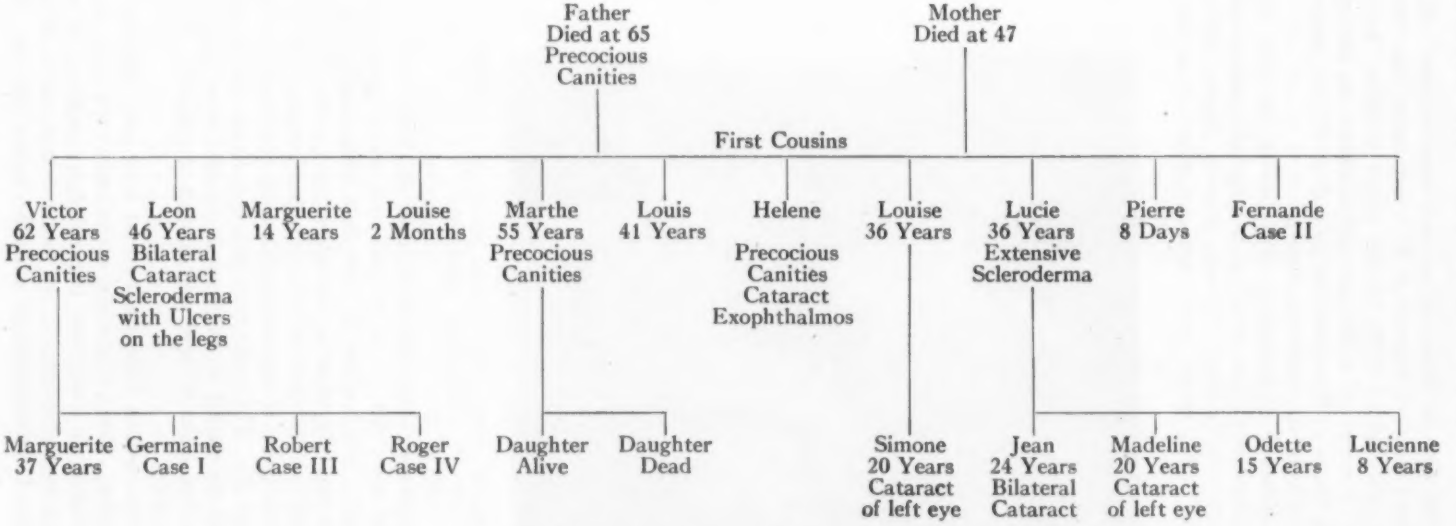
E. M. Barbot,[6] in a Thèse of Paris, in 1925 (the same cases were later republished by *Monier-Vinard and Barbot* [7]) discussed in a paper entitled "La sclerodermie associé à la cataract (affection familial)" a family in which the *grandfather* had early canities, and *cataracts* at the age of 40. The mother observed graying of the hair at the age of 20 and cataracts between the ages of 20 and 30. She did not have any skin changes. This woman had five children. One child died of intestinal troubles. Two sons were healthy. Two daughters showed skin changes, canities and cataracts.

Case 1. Miss Marie C., age 46, height 160 cm. Shell-like plaques of *hyperkeratosis on both soles* beneath the great toe were noticed at the age of 20. The *skin* over the lower legs and ankles was tightly stretched. At the age of 22 the *voice* became hoarse. She was a singer and had to give this up. At the same time the



scalp *hair* began to turn gray and to become sparse. The pubic hairs almost disappeared. When she was 25 *cataracts* developed. At the time of the last examination, 1931, the skin over the ankles and feet was taut and tight. She had difficulty in moving. On the points of pressure on both lower legs *ulcers* and scars of ulcers were present. Both lower *legs* were very thin, almost like a skeleton (Cadavre congelé). Above the knees skin was normal and the muscles better developed. Toenails were atrophic. Menstruation started at 12 and stopped at 44. Tendon reflexes of the lower extremities could not be elicited. Triceps were normal.

Case 2. Miss Martha C., 42 years old. Short in stature. The *skin* changes developed at the age of 25. The *ulcers* are the same even in small details, as seen



Genealogical Table of Family P

FIG. 1.

in her sister. When she was 30, bilateral *cataracts* were evident. Menstruation began at the age of 13 and was still regular at 42. Her voice was clear.

S. Bau-Prussak [8] reported in 1926, in his paper entitled "La dégénérescence génito-sclérodermique," the case of a 36 year old woman. At the age of three the patient's vision was defective. Menstruation started at 18 and stopped at 20. The general habitus of the patient was underdeveloped.

M. Sainton and Mamou [9] described, in 1927, under the title "Syndrome pluriglandulaire avec sclerodermie et cataracte" a 25 year old male metal worker. He had only one brother who was normal. He was short in *stature,* 149 cm. He looked much younger than his age. *Hairs* were rare and gray; there was no mustache.

FIG. 2. *Case 1.* Germaine: Gray scarce scalp hairs; scanty eyebrows; no eyelashes. Presenile appearance.

Eyebrows and eyelashes were sparse as were, also, the pubic hairs. The *ears* stood out from the head and were flat. The *skin* was of waxy color, thin and adherent to the underlying tissue. The motion of both feet was inhibited by the taut, sclerodermatous skin. On the feet were several *ulcer* scars. On the right great toe an active ulcer was present. In contrast to the globulous abdomen the extremities were slender and thin. The toe-nails were atrophic and deformed. Bilateral *cataracts* developed at the age of 22. The *voice* was hoarse. *Endocrine features:* The penis was small. The testes descended at the age of 13 and were small in size. Sella turcica was normal in size. The thyroid was difficult to palpate. There was gynecomastia of the right breast.

T. Hashimoto [10] reported, in 1930, the case of a 44 year old man who developed cataracts and scleroderma. Penis, testes and epididymis were very small.

H. Eguchi [11] published, in 1930, two isolated cases, without history of familial incidence, which belong to this group. A 32 year old man and a 30 year old woman had identical symptoms: 1. Disturbance of growth; height 148 cm. 2. Scleroderma-

like skin changes on hands and feet. 3. Canities (grayness of the scalp hair). 4. Cataracts showed at the age of 28 in the man and at the age of 26 in the woman, star-like densities on the posterior cortex of the lens. 5. Hoarse voice. 6. Retarded development of the sex organs in both cases. 7. Both patients had high blood sugar values. In addition a goiter was present in the female.

The cases reported by *A. Sézarry, Favory and H. Mamou,*[12] published also in his Thèse de Paris, 1931, by *H. Mamou*[13] alone, under the title "Some rare symptoms of scleroderma" do not belong to the group of Werner's syndrome. They do not show shortness in stature, canities, ulcers or presenility, but true scleroderma with melanosis of the skin and cataracts.

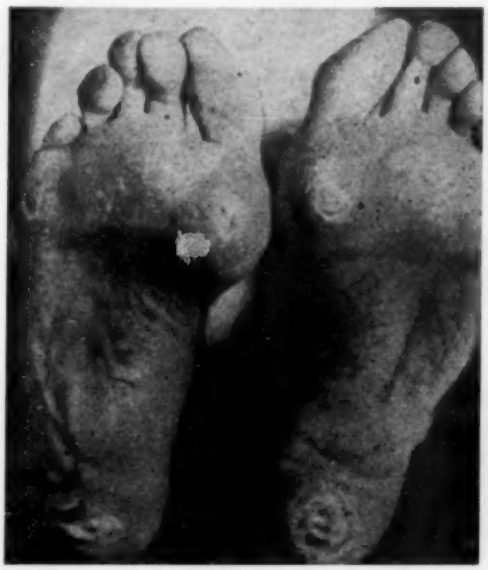


FIG. 3. Shell-like hyperkeratosis on both heels, under the large toe. Ulcers under the fifth toe; hallux valgus.

The most impressive evidence of the heredofamilial occurrence of the syndrome under discussion is found in the description of *E. Krebs, E. Hartmann and F. Thiebaut*[14] of "un cas familial de syndrome de sclerodermie avec cataracte, troubles endocriniens et neurovegetatifs associés."

Case 1. Mrs. Germaine G., née P.; 35 years old; married; no children. *Short stature,* very slender; scanty gray hair in contrast to her young appearance. Scalp *hairs* started to turn gray when she was 18. There were almost no eyebrows and only a few eyelashes. Secondary pubic hairs were short and straight. *Skin:* Scleroderma developed slowly without premonitory edema on the lower legs and feet. The hue of the skin was waxy. For a long time the patient had been able to walk only with difficulty because the skin was very tightly stretched over the ankles and the dorsum of the feet. The feet gave the impression of solid blocks. The skin over both Achilles tendons, over both heels and on the soles under the large toes showed circumscribed areas of extreme *hyperkeratosis* of a corn-like nature. After the hyperkeratotic areas peeled off, deep, non-healing *ulcers* developed. Both large toes were in hallux valgus position. The insteps were very high and the toes were fixed in extensor position. The reflexes were normal. Cataract on both eyes. Opera-

tion performed on cataract of the right eye. There was slight exophthalmos; slight tremor of the hands. The thyroid was not enlarged. *Endocrine features:* Menstruation was always irregular. It started at 12. There were complaints of hot flashes. Basal metabolic rate + 11. No disease of internal organs found. Fasting blood sugar, 88 mg. per cent. Sugar tolerance curve was normal. Cholesterol 170 mg. per cent; calcium 11 mg. per cent. There was no report of roentgenograms of the blood vessels or bones.

Case 2. Miss Fernande P.; 38 years old; aunt of case 1. Short in *stature.* Presenile appearance. *Hair* was already gray at 18. There were almost no eyebrows or eyelashes. Pubic hairs were very scarce and straight. *Skin:* The same

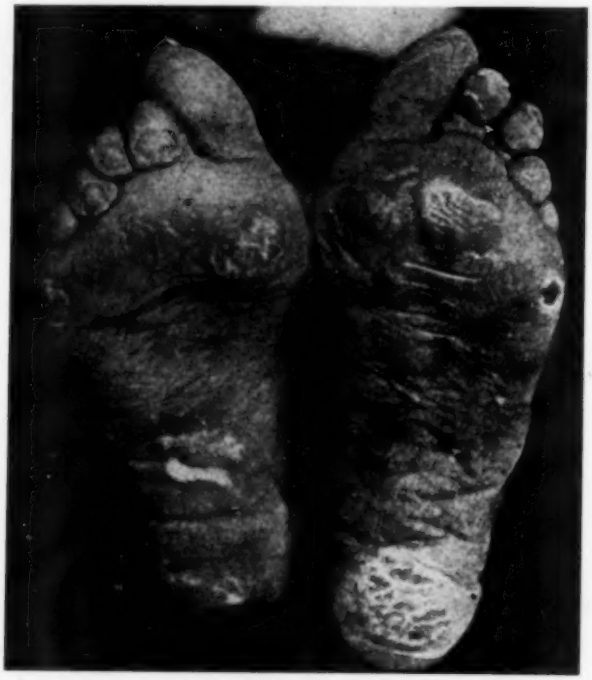


FIG. 4. *Case 2.* Fernande: Note same areas of hyperkeratosis only this time small ulcer under left toe.

changes with circumscribed hyperkeratosis and ulcers as described in case 1 were found. The phalanges of the toes were fixed in a flexed position in contrast to the extensor position of case 1. Both large toes were in hallux valgus position. The skin was more scaly and itching. Bilateral *cataracts* were operated upon at the age of 30. *Endocrine features:* Slight exophthalmos. Palpitation at a rate of 100 was noted. Thyroid was not enlarged. Basal metabolic rate + 16. Menstruation was regular. Mammae very small. Hot flashes. Sella turcica normal in size. *Vascular system:* Heart—no disease was noted. Roentgenogram showed the aorta distended and slightly sclerotic. Wassermann reaction was negative. Fasting blood sugar, 88 mg. per cent. Sugar tolerance normal. Total cholesterol 260 mg. per cent.

Case 3. Robert P.; 29 years old; brother of Germaine, case 1. Short in *stature,* 151 cm. Weight 45 kg. Gray, scarce scalp *hairs.* Pubic hairs very rare. Body hairless. The nose was beaked. The chin was small and retracted. The ears were

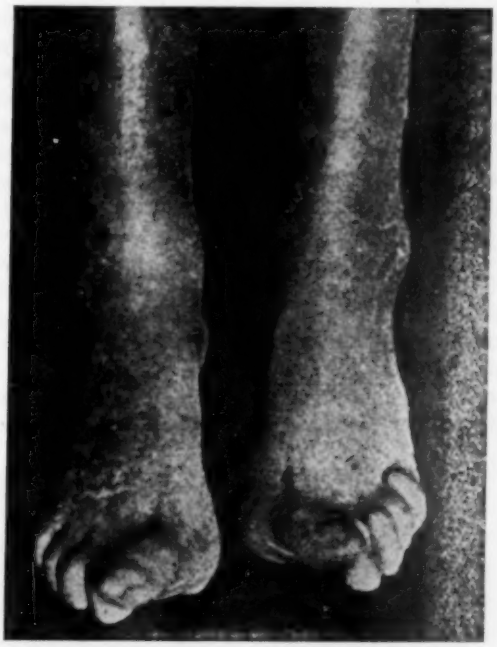


FIG. 5. Skin tightly stretched over ankles and toes. Note healed ulcer under the left malleolus.

FIG. 6. *Case 3.* Robert. Large ulcer on left inner malleolus.

very small; the auricles were flat but projected from the head. The *skin* over the forehead was taut, without folds. The skin on the forearm and hands was tightly stretched. The hands were small and the fingers were short and crooked and of nodular appearance. A similar shape of the fingers was also observed in cases 1 and 2. The skin over the lower legs and feet was atrophic and of wax-like appearance.

The skin on these parts was so tightly stretched that any motion in the ankle joints was difficult. The underlying *muscles* were so thin they gave the lower legs and feet a skeleton-like appearance. Both large toes were in hallux valgus position. The toes were fixed in extension position. Numerous *ulcers,* old and new ones, were present on the points of pressure. An especially large ulcer was located on the inner malleolus. A few telangiectases were observed on the base of the thorax. *Cataracts* were present in both eyes. The *voice* was hoarse and high pitched. *Endocrine features:* The thyroid was not palpable. Genital organs were small and underdeveloped. The right testicle was ectopic; the left testicle was small. Genital functions were reported as normal, but probably developed late. *Vascular system:* The heart was reported as normal. Pulse rate was 90. Blood pressure was 130 mm. Hg systolic and 80 mm. diastolic. No report of calcification in the arterial wall was made. The *spleen* was of normal size. Tendon reflexes were normal, as was the sensibility. Fasting blood sugar, 116 mg. per cent. Sugar tolerance test produced glycosuria. Sugar tolerance curve was that of a potential diabetic. Calcium 9.9 mg. per cent. Total cholesterol 90 mg. per cent. Basal metabolic rate + 13.

FIG. 7. *Case 4.* Roger. Small hands; deformed phalangeal joints. Presenile appearance.

Case 4. Roger P. is the tallest of his family—167 cm. He presented the same general presenile aspect as his brother. The forehead was smooth, without wrinkles, the nose was thin, the chin was small and retracted, the ears were flat and projecting. The face resembled that of a mummy. The *skin* had features similar to those of his brother Robert, but to a lesser degree. Scars of *ulcers* were visible on the points of pressure (over elbows, heels and ankles). On the lower part of the thorax the skin showed the same telangiectases as did that of his brother. Scalp *hairs* were of an indefinite grayish color and scarce. Eyebrows were present. Pubic hairs were

almost absent. *Cataracts* were developing in both eyes. Teeth showed malformation, especially on the superior incisors. *Endocrine features:* The penis and the testicles were very small. Puberty was late. Intercourse was sometimes carried out. Slight exophthalmos. *Vascular system:* The heart was normal. Blood pressure was 130 mm. Hg systolic and 80 mm. diastolic. Pulse rate was 102. The skin changes were the same as in all the cases reviewed above and characteristic for the heredofamilial dermatosis in Werner's syndrome, but not of true scleroderma. All cases examined of family P. were short in stature and abnormally lean. Especially the lack of subcutaneous tissue in the distal parts of the extremities gave the lower legs a skeleton-like appearance. Hallux valgus formation was noted in all members of this family. Hands and feet were abnormally small and short. The chin was small and retracted. The small size of the hands and feet and the small retracted chin, in contrast to their large size in acromegaly, is justifiably called acromicria. Slight exophthalmos with and without goiter formation, but without definite signs of hyperthyroidism is reported in some members of family P. Hypogonadism, however, is observed in all four cases exhibiting the complete syndrome under discussion.

Comment. In addition to these four cases of the family P., examined by the authors personally, the history of the whole family is revealed in the family tree.

The syndrome under discussion was present in all its features in three members of the second generation (Leon, Louis, Fernande) and in three members of the third generation, but some features of the syndrome (canities, scleroderma-like skin changes and cataracts) occurred interchangeably as abortive features (forme fruste) also in other members of the family in three generations. These observations are of great importance since they prove: first, a recessive inheritance of the syndrome; second, that abortive features of the syndrome may occasionally occur as "forme fruste" easily overlooked by physicians not familiar with this peculiar heredofamilial disorder.

B. S. Oppenheimer and V. H. Kugel [15] reported, under the title "Werner's syndrome," three cases with photographs and the autopsy findings. Two of these were brothers.

Case 1. D. G., male, 48 years old. *Grandparents* and *parents* were *first cousins. Stature* was short; height 149 cm. Weight was 118 pounds. At the age of 12 premature graying of the scalp *hairs* and loss of scalp hair were noticed. At 48 he was bald, only sparse hairs being present on the scalp. Pubic hairs were sparse. Chest hairs were abundant, but gray. On the extremities hairs were absent and sweating was diminished. The *skin* of the entire face, part of the scalp and back of the ears was distinctly abnormal but not so markedly altered as in the extremities. The normal luster, smoothness and pliability were replaced by thickening, roughness and loss of normal elasticity. The mouth was abnormal, small, surrounded by fine rhagades, and could not be opened easily. In the extremities the changes were most marked distally and gradually regressed to merge imperceptibly into apparently normal skin, at the upper third of the legs and forearms. There were circumscribed areas of *hyperkeratosis* on the plantar surfaces of both feet and over the very taut scar at the site of the amputation of the left foot. The skin of the feet was atrophic, smooth, glistening and taut and impeded the motion of the joints of the toes. There was an edematous appearance of the feet, but no pitting on pressure. There were numerous scars of old ulcerations, some surrounded by areas of pigmentation, over

both malleoli and plantar surfaces of the toes. There was an indolent, non-erythematous ulceration, the size of a quarter, over the right external malleolus, and there were several other ulcerations around the right ankle and over the dorsal surface of the toes of the right foot. There were also a few fine telangiectases. The skin of the hands and fingers was more typically "sclerodermatous." It was thickened, wrinkled, in places adherent with marked loss of elasticity. Over the olecranon were patches of hyperkeratinization. On the forearm the skin was atrophic and taut. The nails of the toes showed advanced atrophic changes, i.e., hyperkeratinization, deformation and discoloration. The nails of the fingers were brittle and revealed numerous longitudinal striations. *Biopsy of the skin* "shows marked atrophy of the epidermis. Papillae are flattened. Underlying tissue is hyalinized. Calcium stain is negative. Histological picture is consistent with the diagnosis of scleroderma" (Dr. Perla). *Joints:* The small joints of both feet were immobile owing to the taut skin stretched over them. There was limited motion of the ankle joints. There was normal mobility of the larger joints of the body. Left foot showed productive arthritis. Small exostoses were present. Both feet were flat and everted with

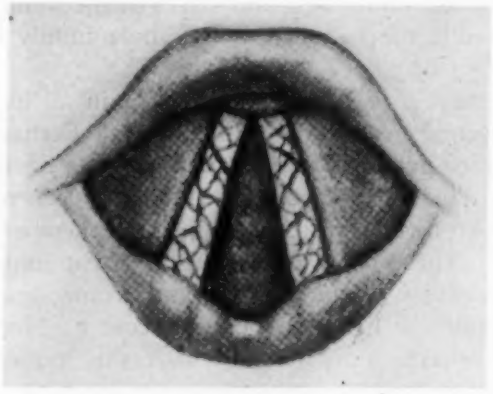


FIG. 8. Picture of vocal cords. (Reproduced from B. S. Oppenheimer and V. R. Kugel.)

hallux valgus formation. The contrast between the well developed chest and trunk and the thin, slender "juvenile" extremities was striking. The bones of the arms and legs were thin. The subcutaneous fat and the muscles were underdeveloped (especially on both lower limbs and forearms, according to the photograph). *Osteoporosis* of the osseous system was seen by roentgenogram. *Blood vessels:* Calcification of the medium-sized arteries was visible in different parts of the extremities in roentgenograms. *Eyes: Cataracts* in both eyes had been operated upon. The cataracts developed at the age of 36. *Teeth* were normal and not decalcified. *Voice* was high pitched and husky. *Larynx:* (S. R. Kramer) "Overhanging epiglottis. On the upper surface of the vocal cords there are white areas, irregular in size and shape, separated from one another by bands of varying width of pinkish red mucosa. These reddish strands are made up of dilated vessels in the midst of congested mucosa and extend into the ventricles and on the free edges of the vocal cords. The whole picture is a bizarre one of variegated shape and color. There is slight thickening of the edge of the right cord in its midportion, due to an area of injection." *Vascular system:* The patient complained of precordial pain relieved by nitroglycerin. A blowing systolic murmur was heard over the cardiac area. Blood pressure was 168 mm. Hg systolic and 90 mm. diastolic. Roentgenogram showed cardiac enlargement and

calcified deposits in the arch of the aorta. *Endocrine glands:* The thyroid was not enlarged. Basal metabolic rate was — 12, — 19, — 5. Fasting blood sugar was 85 mg. per cent. Sugar tolerance test showed a flat curve. No glycosuria. Blood calcium was 9.9–10.0 mg. per cent, phosphorus 2.5–4.2 mg per cent, phosphatase 7 Bodansky units. Calcium balance was normal. Testes were normal in contour and consistency, but reduced in size. The penis was underdeveloped. Libido and potency were claimed to be normal. Neurologic status showed no abnormality.

Case 2. A. G., a 30 year old man, brother of D. G., was short in *stature*. Height was 147 cm., weight 131 pounds. In general appearance he resembled his brother so closely that they were often taken for twins. Although six years younger than his brother, on the whole he looked older. The general habitus, premature senility, thin, slender extremities, flat and everted feet, hallux valgus formation, were the same in both patients. Scalp *hairs* started to turn gray at the age of eight. At the age of 20 he began to lose his scalp hair and at 22 he was noticeably bald. Hair over the chest and abdomen was sparse. The distribution of the pubic hair was feminine in type. *Skin:* Although the distribution of the changes of his skin was identical with that of his brother, the predominating features were atrophy and telangiectases, so that dermatologists, from inspection of his skin alone, would emphasize the poikilodermatous rather than sclerodermatous character of the change, whereas in his brother the scleroderma predominated. In his lower extremities he also presented cutis marmorata. The ulcerations were more numerous, more extensive and more persistent than those of his brother. There was a shallow ulcer, due to pressure, over his left elbow, about 3 cm. by 1.5 cm., exposing the periosteum. Telangiectases on knees and scrotum were prominent. He was admitted to the hospital several times because of his ulcers. Secondary infection and cellulitis made an amputation of the right big toe and metatarsal bone necessary. *Skin biopsy:* (S. M. Peck) "The epidermis is thin throughout most of the section. The normal rete pegs have disappeared. There is a moderate hyperkeratosis with no parakeratosis. The epidermis has for the most part been reduced to six layers. The stratum granulosum is only one layer thick. The basal cell layer shows scattered areas of edema; many of the cells are reduced in size, seem shrunken, whereas others show intracellular edema and even formation of vacuoles in the cytoplasm. Many of the basal cells contain a fairly good amount of melanine arranged in 'cap' formation over the nuclei. No dendritic cells are seen. The papillary bodies are flat. Scattered through the upper layers of the cutis are a few dilated capillaries with very little, if any, perivascular infiltration consisting mostly of lymphocytes. The sebaceous and sweat glands are reduced in number but appear unchanged. The cutis is very poor in cellular elements. The elastic tissue has mostly disappeared and where it is present it is fragmented and torn. In places the collagen fibers themselves take a basophilic stain and seem to have undergone degenerative changes. The sections certainly seem to fit in with the picture of poikilodermia atrophicans. But there are also some elements which fit in with the picture of scleroderma, especially the atrophic stage of that disease. The histologic picture which I have described seems to parallel that of Bloch in his cases." *Joints:* Lower and upper extremities, especially on the phalanges of the small hands and feet, ankles and wrists, showed productive arthritic changes similar to those of his brother. Slight arthritic changes were also seen on the roentgenograms of pelvis and spine. *Osseous system:* Diffuse osteoporosis like that of his brother. *Blood vessels:* Calcification of the medium sized arteries, in different parts of his extremities, was even more marked than in the roentgenograms of his brother. *Cataracts* had developed in both eyes. The left eye had already been operated upon. Marked proptosis of both eyes was noted, without signs of hyperthyroidism. He lost 20 *teeth* in the last year; the remaining teeth were loose owing to absorption of the alveolar bone rather than to caries. The *voice* was high pitched and husky like that

of his brother. Also the bizarre and characteristic *laryngoscopic picture* was the same as in his brother. *Vascular system:* Blood pressure was 140 mm. Hg systolic and 90 mm. diastolic to 170 mm. systolic and 100 mm. diastolic. Electrocardiogram showed left axis deviation but no other changes. On his first admission no enlargement of *liver and spleen* was found. On his third admission liver and spleen were found to be greatly enlarged. Ascites was present. The diagnosis of a hepatic neoplasm was made and verified at necropsy. *Endocrine features:* The thyroid was not enlarged. Metabolic rate was between − 24 and − 6. Fasting blood sugar was 153 mg. per cent. Sugar tolerance curve was characteristic of potential diabetes. There was no glycosuria. Blood calcium was 10.6–13.1 mg. per cent. Hamilton test was positive. Blood phosphatase showed 4–8 Bodansky units. Calcium balance was within the range of normal. Both *testes* were small. Hypogonadism was evident. In contrast to his brother he was of normal intelligence. The patient died of a terminal pneumonia. The *autopsy* confirmed the diagnosis of a primary liver carcinoma and is reported in detail in *B. S. Oppenheimer and V. H. Kugel's* paper.[16] The chief abnormal findings were calcification of the mitral and aortic valves, diffuse arteriosclerosis of Mönckeberg's type, status after bilateral cataract extraction, diffuse osteoporosis, moderate metastatic calcification in skin, kidneys and vessels. Endocrine glands: (examined by D. Marine) "The testes, seminal vesicles and prostate gland were very small. The aspermatogenesis and atrophy of the testes were premature. The adrenals are large with multiple cortical adenomata, the glomerular zone is active (whereas the glomerular zone in older people is usually ill-defined). The thyroid must have passed through cycles of increased and decreased activity to account for the multiple adenomata. The pituitary showed no abnormality. Parathyroids showed increased activity." Skin showed the same findings as reported in the previous biopsy.

Case 3. H. T., male, 38 years old. *Parents were first cousins.* The father's sister had a daughter with short extremities. The patient was born in Hungary in a district not far removed from the place where the ancestors of both brothers (case 1 and case 2) lived, but the families were not related as far as could be ascertained. He was well until 1926. Injury to his left heel caused a foot drop. At this time he developed various cracks in the skin of the foot which took a long time to heal. By 1937 *ulcers* of the left foot appeared with shortening of the Achilles tendon. In 1937 he had an ulcer on the right heel. The toes of his feet gradually became immovable and the skin became hard, dry and shiny. In 1937 a new growth on the radius of the left forearm was detected. The mass was removed in 1938 and histologically diagnosed as fibrosarcoma. *Appearance:* Although actually 38 years old, he was generally taken for 45. He was short in *stature*. His height was 157 cm.; his weight 52 kg. The same bizarre discrepancy in the size of the large and even fat torso and the thin and gracile extremities could be seen in the published photograph. The hands were very small. The graying of the hair began at 18. At 38 he was partly bald and gray. The hair over the chest and abdomen was sparse. The distribution of pubic hair was feminine in type. The *skin* was drawn tightly over the shins and wrists and presented many areas of pigmentation, discoloration and dry scales. There were a few telangiectases of the *skin* over the knees and feet. A foul-smelling necrotic mass overlaid the left radius. A pressure *ulcer* was found over the right elbow and a crusted ulcer was seen over the right malleolus. Severe ulcerations and pigmentations were present on both feet. The skin of the toes was dry, hard and so taut that the toes could not be moved. The left ankle was fixed in extension, the knee could not be fully extended and the right ankle had slight power and movement. There were prominent veins over the thorax and extremities. The *vascular system* showed advanced sclerosis of the blood vessels of the upper and lower extremities. No pulsation of the dorsalis pedis or posterior tibial arteries could be felt.

The heart was not enlarged. There was a systolic murmur over the aortic area. Blood pressure was 180 mm. Hg systolic and 108 mm. diastolic. Electrocardiogram showed a left axis deviation. The *eyes* were prominent and staring. The sclerae were blue. There was bilateral postoperative coloboma of the iris. *Cataracts* in both eyes were present. They appeared at the age of 31. The cataract of the right eye was operated upon at the age of 38; the cataract of the left eye was operated upon earlier. The *teeth* began to loosen at the age of 33. The remaining teeth were carious. The *voice* was high pitched. Liver and spleen were not enlarged. *Osseous system:* Generalized osteoporosis was found by roentgenogram. *Endocrine features:* The thyroid was not enlarged. Basal metabolic rate was −5 and −8. Total cholesterol 167 mg. per cent, cholesterol esters 111. Fasting blood sugar 87 mg. per cent. Glucose tolerance curve was rather flat but within normal limits. Serum calcium was 10.3 mg. per cent, serum phosphorus 3.9 mg. per cent and phosphatase 6 Bodansky units. Hamilton test was positive. The genitalia were small. The prostate was very small and smooth and felt about one-third normal size. A mild degree of gynecomastia was present.

Comment. Oppenheimer and Kugel published a family tree of both brothers D. G. and A. G. Like the genealogic table of the family P. reported by E. Krebs, E. Hartmann and F. Thiebaut, the occurrence of the syndrome in some members with incomplete features (forme fruste) is evident. In the family G. usually canities appeared in members of different generations as the outstanding feature, whereas in the family P. reported by the French authors, the juvenile cataracts occurred in members of different generations as the outstanding symptom. The skin changes of the three cases of Oppenheimer and Kugel are designated as "sclerodermatous" as the earlier authors did in their cases, or as "poikilodermatous," especially in the case of the younger brother, A. G. The question of the presence of true scleroderma is of great importance, since this type of skin disease was ascribed to a primary hyperfunction of the parathyroids. The present conception of the etiology of true scleroderma is based on the histological picture of skin biopsies which exhibit as characteristic features: 1. Homogenization and sclerosis of the subcutaneous tissue, and 2. Inflammatory changes of the arteries of the subcutaneous tissue revealing perivascular infiltration and obliterative vascular changes. Neither of these characteristics was prominent. Vascular infiltration and obliterative changes were absent. The pathogenetic connection of diffuse scleroderma with hyperfunction or hypertrophy of the parathyroids is abandoned in the newer literature in favor of a pathogenesis due to inflammatory involvement of the blood vessels of the subcutaneous tissue. Even if the tight and taut appearance of the skin simulates scleroderma in the cases under discussion the histologic features do not bear out the presence of true scleroderma. In case 2, A. G., the histological diagnosis pointed to poikiloderma vasculare. Indeed the lesions with telangiectases are very suggestive of this type of skin disorder first described by Jacobi. B. Bloch, however (see page 605), hesitated to designate this skin lesion as identical with real poikiloderma or poikiloscleroderma. It is possible, therefore, only to designate these peculiar atrophic skin lesions

by a simple descriptive name such as "atrophic heredofamilial dermatosis with skin ulcers." It does not seem appropriate to attach a dermatological classification already in use for the designation of well defined inflammatory skin diseases to a heredofamilial disorder.

Oppenheimer and Kugel [16] express the opinion that the syndrome described by Rothmund in 1868 is essentially different from the cases of Werner and their own cases. We agree with the authors that there are

FIG. 9. Nathan O. and Sidney O. Short stature; presenile appearance.

definite differences between the adult cases of Werner and the children described by Rothmund, but one is bound to admit that the follow-up study by R. Seefelder of Rothmund's cases during their adult life, as well as the later description of other adult cases of Rothmund's syndrome, bears out the close relationship of Werner's and Rothmund's syndrome. Further classification of the differences and similarities in Werner's and Rothmund's syndromes will be offered in the second part of this paper.

OWN OBSERVATIONS

The brothers, Sidney O., 38 years old, and Nathan O., 34 years old, were born in the United States of Russian Jewish parents. Both parents were healthy. They

came from different towns in southern Russia and were not related. Both paternal and maternal grandparents were healthy and lived to an old age. No interrelationship of any ancestors or any occurrence of a similar disorder in this family is known.

Case 1. Sidney O. was born a normal child. He went to high school and later to a pharmaceutical school. After graduation he practiced pharmacy. He was very intelligent, well read, and wrote poetry. *Appearance:* He was short in *stature*—five feet three inches (168 cm.); weight 120 pounds. There had been no recent weight loss. He looked like an old man, about 20 years older than his actual age. The scalp *hairs* began to turn gray at the age of 15. They became sparse at the age

FIG. 10. Fine, scarce, gray scalp hairs; beaked noses; small mouths.

of 20. They now looked like the hairs of a mouse suffering from food deficiency, being fine, sparse and of an indefinite grayish color. He had fine, scarce hairs on the upper lip and on his face. He shaved twice a week. The hairs on his body were scanty and gray. On the lower arms and legs, where the skin changes were most outstanding, there were no hairs at all. On these hairless areas of the extremities perspiration did not occur. The sex hairs were scarce and rudimentary, most of them being straight like bristles. At the age of 21 he noticed circumscribed areas of *hyperkeratosis* under his big toes, under his heels, on both lateral parts of his feet, as well as on his insteps. At the time of his admission to the hospital these areas of hyperkeratosis were slightly elevated above the surface of the skin and consisted of cornified, horny layers, which gave these areas a shell-like appearance. The patient reported that the removal of these "corns" resulted always in an ulcer which did not heal for a long time. The *skin* of the face was taut but not tightly fixed on the underlying structures. Beneath the eyes, especially on the nose and nostrils, the skin was not tightly stretched as was seen in true scleroderma. The opening of his mouth was not hampered although the aperture was small. On both sides of the face there were two distinct, symmetrical areas of fat accumulation. A similar fat deposit was found in the region of the parotid gland and over the horizontal part of the mandible. The subcutaneous fat in other parts of the face was rather poorly developed. The skin over his lower legs and feet showed the most characteristic changes. Starting downward from the knees the skin appeared taut and tightly stretched over the underlying structures and over the ankles and insteps became so

tightly adherent to the underlying tissue that the motion in the ankle joints and phalangeal joints was grossly impaired. Large *ulcers,* the size of a silver dollar, were present over both Achilles tendons. Several smaller ulcers were found over the malleoli, the lateral surfaces of the feet and between the large and second toes. The ulcers seemed to be located on parts exposed to pressure. The patient himself reported that the ulcers appeared first at the age of 24 and healed very slowly or not at all, draining a thick fluid. Most of the ulcers were covered with a thick, greenish, fibrinous membrane. The ulcers had been painful, especially at night, to

FIG. 11. Sidney O. The small, thin upper arms and lower legs in direct contrast to globulous abdomen.

such a degree that morphine had to be given. Besides the active ulcers there were many scars from healed ulcerations. Both large ulcers over the Achilles tendon were grafted by Dr. E. Cooney; the grafts healed.* Slight linear pigmentation of a light brownish color together with some scaling along the pigmented lines was noted. There were no telangiectases. The skin over the phalanges had a reddish hue, whereas the color on all other areas involved was whitish and waxy. There was no pitting on pressure. The skin on the lower parts of the arms and hands was also taut, but not so tightly stretched over the underlying tissue as on the lower legs and feet. On the dorsal surface of the hands the thin, atrophic skin was even pliable, like tissue paper, whereas over both wrists the skin was tightly drawn. The circum-

* After six months a new ulcer started on the edge of the graft.

ference of the wrist was 14 cm.; of the upper arms 20 cm.; of the calf 24 cm.; and of the ankles 16 cm. In these parts of the body the *subcutaneous fat tissue* was extremely scanty. One got the impression that this lack of subcutaneous fat paralleled the atrophy and tightness of the skin. The *muscles* of the distal parts of the ex-

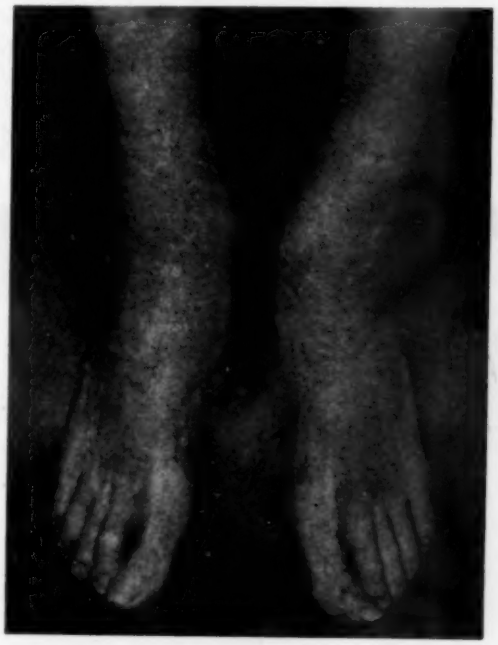


FIG. 12. Sidney O. Taut skin tightly stretched over underlying tissue; motion impaired in both ankle joints; hallux valgus. Ulcers on left inner malleolus, on lateral sides of feet.

FIG. 13. Large ulcers on Achilles tendons.

tremities were thin and poorly developed, but there was no restriction of motion due to paresis or paralysis of the muscles. Where there was restriction of motion it was the result of the tightly stretched skin. Both feet were extremely flat and everted with hallux valgus formation. The phalangeal *joints* of the hands and feet showed

thickening of the periarticular tissue as seen in arthritis. All the toes were small and immobile. The *toe-nails* were present but atrophic. The finger-nails were short. The patient reported that they grew very slowly. The arms and legs, as a whole, appeared extremely thin and gracile. The small hands and feet, lacking any fat tissue, in contrast to a rather round abdomen, gave the extremities a grotesque appearance. Roentgenograms of the bones, especially of the arms where the dermatosis is evident, showed severe *osteoporosis*. In the same roentgenograms the arteries of the lower legs and feet showed calcification due to arteriosclerosis. The arterial pulse could not be felt in either dorsalis pedis artery. Arteriosclerosis, but to a lesser degree, also involved the arteries of the upper arm. *Eyes:* (Note of Dr. J. J. Skirball) "*Cataract* extraction, left eye, 1936, eight years ago. Right eye, 1939, five years

FIG. 14. Healed ulcers of Achilles tendons after grafting.

ago. Some capsular remnants. Patient has had a secondary iridotomy. Fundus: Disk is of good color, the margin is clear, no elevation of the disk is seen. The arteries are moderately narrowed and slightly angulated, also veins are slightly narrowed. The changes on the arteries indicate early arteriosclerosis. There is definite proptosis of both eyes; no lid lag." The nose was small and beak-shaped; the nostrils were freely movable. The *chin* was small but not retracted. The ears were small, but flat and protruding laterally from the head. The drums were very thin and almost atrophic. Hearing was good in both ears. *Voice* was high pitched. *Laryngoscopic findings* did not show any abnormal change. *Teeth* had all developed and were in fairly good condition. The *chest* was of normal diameter. The *lungs* were normal. The *heart* was normal in size; no murmurs were heard. Blood pressure was 125 mm. Hg systolic and 85 mm. diastolic. *Endocrine features:* The short stature, the general senile appearance and canities have already been mentioned. The thyroid was not enlarged. The proptosis of the eyes was not a true exophthalmos. There was no lid lag. There were no features of hyperthyroidism. Basal metabolic rate was −15. Total cholesterol was 172 mg. per cent; free cholesterol 39.5 mg. per cent; ester cholesterol 132.5 mg. per cent. The penis was very small in size. The two testes were descended but were of small size. The prostate was small. His sexual desire was not very strong. He sometimes had ejaculations. He was not married. Follicular stimulating hormone in blood was reported negative; 3.24 mg.

of 17 ketosteroids per 24 hours were excreted. Creatine was 0.8–0.61 mg. per cent in 24 hour urine. Sugar was present in traces. Sugar tolerance curve: fasting 150 mg. per cent; one-half hour 274 mg. per cent; one hour 286 mg. per cent; two hour 278 mg. per cent; three hour 272 mg. per cent. Calcium was 11.8 mg. per cent; phosphorus, 3.6 mg. per cent; alkaline phosphatase, 2.2 Bodansky units. Other laboratory findings: Total serum protein was 8 gm. per 100 c.c.; albumin, 5.5 gm.; globulin 3.2 gm. Blood sedimentation rate was 28 mm. in 20 minutes, 74 mm. in one hour. (Blood sedimentation rate was increased, probably owing to ulcers of the leg.) Wassermann and Hinton reactions were negative. Hemoglobin was 75 per cent, red blood cell count 2.24 million per c.c.; color index 0.9. Leukocytes were 10,000 per mm. Differential count: Band forms 5 per cent, adult neutrophiles 63 per cent, eosinophiles 3 per cent, basophiles 1 per cent, lymphocytes 16 per cent, monocytes 12 per cent. Platelets were normal. The appetite of the patient was excellent. In the hospital he consumed a diet of 2500 to 3000 calories without gaining weight.

Case 2. Nathan O., 34 years old, had the same schooling as his brother Sidney. He also graduated from a pharmaceutical school in Providence and practiced thereafter with his brother, as a pharmacist in his own drug store. He was intelligent, also, but had less literary ambition than his brother. As a boy, until he was 16, his maximum weight was 140 pounds. At the age of 20 he lost considerable weight. This weight loss was believed to be due to hyperthyroidism. The patient was told that he had an internal goiter, but only a slight external one. A subtotal thyroidectomy was done when he was 21. After the operation he lost further weight. It was then discovered he had diabetes. He was put on insulin and his diet was regulated. He controlled his treatment himself and the urine was sugar free for years. In July 1943 his left foot became infected and gangrene of the second and third digits developed. It was thought that this infection was due to a diabetic gangrene, but apparently the infection and gangrene developed from an infected ulcer. An amputation below the left knee was performed by Dr. L. S. McKittrick. The pathological report (Dr. B. Castleman) was: "Advanced arteriosclerosis, thrombosis and recanalization. Gangrene with fistula formation." After the patient came under our observation Dr. McKittrick sent us the following note: "His whole appearance is unusual. His skin is inelastic . . . almost that of a patient with scleroderma. He did not do as well after his amputation as most patients do in that there was a small area that necrosed." He was put on an 1800 calorie diet with 25 units protamine zinc and 10 units regular insulin. Six months later the patient was admitted to our hospital. At this time the 24 hour urine contained 8–10 gm. sugar. *Appearance:* He was short in stature, five feet and three-quarters inches (144 cm.); weight: 93.5 pounds. His likeness to his brother was surprising. Many people considered the brothers twins. His face, however, was not as full as his brother's. The fat pads over the parotid and on the lower mandibular region, as seen on Sidney, were not present on Nathan's face. He looked much older than his actual age. The general impression was that he appeared even more senile than his brother. The scalp *hairs* began to turn gray at the age of 16. They were now the same indefinite grayish color as seen on his brother. They were also fine in texture but very scarce. The hair of his face was more abundant than that on his brother's face. He had to shave almost every other day. Also, the hair on chest and abdomen was better developed. The distal parts of both extremities were hairless. The pubic hairs were poorly developed, not curled, but straight and short. The patient noticed the first changes in his skin at the age of 20. "Corns," i.e., circumscribed areas of *hyperkeratosis*, developed on both heels, on the lateral parts of his feet and under the large toes. The hyperkeratotic areas were prominent over the skin and had a shell-like configuration consisting of horny layers. *Skin ulcers* appeared on the points of pressure on the malleoli, on the lateral parts of his feet and on the left instep and over the left second

and third toes. Apparently a secondary infection developed in 1943 from the ulcers of the toes which resulted in an amputation below the knee of the left leg. At present a large ulcer, the size of a quarter, was present on the inner side of his right foot, causing excruciating pain, usually during the night. Opiates were necessary every night to relieve this pain. The skin over the Achilles tendon, unlike that of his brother, was not ulcerated. A smaller ulcer developed on the skin of the right second digit where it pressed against the skin of the large toe. The skin of his face was taut but wrinkled. Long, stiff, nasolabial folds gave his face an old appearance. The

FIG. 15. Nathan O. Amputated left leg. Taut skin tightly stretched over the right lower leg. Ulcer on the inner side of the foot.

aperture of his mouth was small. The skin over the stump of his left leg was normal on the thigh but around the knee, just over the amputation, the skin was atrophic. The pressure of the prosthesis had caused reddening of the skin. (Ulcer formation on the lower end of the stump was feared.) The skin over the right lower leg showed the same characteristics as his brother's. The skin from the knee down was taut, atrophic, and stretched over the ankle and metatarsal joints. Scaling and slight linear pigmentation were visible. Motion of the right foot was limited because of the tightness of the skin. He was able to walk with the help of two sticks, when the prosthesis was in place. The *subcutaneous fat tissue* and the *muscles* of the right leg from the knee down were extremely poor. Circumference of the right ankle was 18 cm. Circumference of the left calf was 23 cm. The skin on both upper arms and hands was taut, but not so tightly pulled over the wrist that it could not be wrinkled.

The texture of the skin was thin and atrophic. The subcutaneous fat was almost lacking on both upper arms and the muscles were very thin. Circumference of the wrists was 12.5 cm. Circumference of the upper arms was 20 cm. The *joints* had the same appearance as presented by his brother Sidney. Roentgenograms of the osseous system, especially of the extremities, showed *osteoporosis*. The arteries of the right leg were extremely calcified. That those of the left leg were in a similar state was confirmed by the pathological examination after amputation. *Arteriosclerosis* was more advanced than in the case of his brother Sidney. Both cataracts had been extracted. The patient had had a secondary iridotomy. The fundi showed changes characteristic of arteriosclerosis. The *ears* were small and flat, protruding laterally from the head. The inner ears were normal. His nose was somewhat longer than his brother's. The nostrils were freely movable. The *chin* was small and slightly retracted. The *voice* was high pitched and husky. *Laryngoscopic findings:* (Dr. Kelemann): "Even after anesthesia only two-thirds of the larynx is seen because the large, flat epiglottis covers the other third. The right side of the larynx is normal. At the left side the vocal cord is covered in its central part by a diffuse red structure moving with the vocal cord. This structure may consist of distended veins or may consist of an hemangiomatous structure. The mucosa of the left ventricle is prolapsed. The arytenoid movements are free as are the other movements of the larynx." *Vascular system and heart:* As has already been stated, the roentgenograms showed sclerosis of the arteries of the right leg. The examination of the amputated left leg showed, as above stated, severe arteriosclerosis. The heart was of normal size. There were no murmurs. Action was regular. Blood pressure was 160 mm. Hg systolic and 90 mm. diastolic. Liver and spleen were not enlarged. *Endocrine features:* His short stature and presenile appearance have already been described. His thyroid was not palpable; the scar of a partial thyroidectomy was visible. His eyes were protruding but there was no lid lag or other symptoms which would indicate hyperthyroidism. Basal metabolic rate was ± 0. The testicles were descended but small. The scrotum was very small, the size of that of a 10 year old boy. The penis was short. (Sexual desire was minimal but ejaculations did occur. He had never had intercourse.) The excretion of total 17 ketosteroids was 5.8 mg. per 24 hours. Sella turcica was within normal limits. His fasting blood sugar ranged between 205–251 mg. per cent. The patient excreted 8–10 gm. of sugar, in spite of receiving 25 units of protamine zinc and 10 units of regular insulin, and a diet of 1,800 calories (170 gm. carbohydrates; 85 gm. protein; 87 gm. fat). Other laboratory findings were: 75 per cent hemoglobin; 4.44 million red blood corpuscles per cu. mm.; color index 0.87; leukocytes 9,800 per cu. mm. The differential count was normal. Total serum protein, 8.08 gm. per 100 c.c., albumin, 5.26 gm., globulin, 2.82 gm. Blood sedimentation rate was 75 mm. in one hour. Blood Hinton reaction was negative. Creatine excretion was 1 gm. in 24 hours. Blood calcium was 11.8 mg. per cent, phosphorus 3.6 mg. per cent, alkaline phosphatase 2 Bodansky units.

Comment. The two brothers not only looked alike but had the following characteristics in common: (1) Shortness of stature; (2) atrophy of the subcutaneous fat tissue and the muscles of the lower arms and lower legs, hands and feet; (3) small hands and feet; (4) canities (premature graying of scalp hair); (5) scarce scalp hairs; (6) atrophic dermatosis of lower legs, feet, upper arms and hands, partially on face; (7) pressure ulcers on exposed parts of the feet; (8) circumscribed areas of hyperkeratosis on feet and insteps; (9) arteriosclerosis of the arteries of the extremities; (10) osteoporosis; (11) diabetes or potential diabetes; (12) hypogonadism and reduced sexual desire. The description of other cases in the literature is so

similar in most of the detailed features that there is no doubt that this syndrome first described by O. Werner is a clinical entity. It is evident from the family trees, especially from that published by E. Krebs, E. Hartmann and F. Thiebaut [14] (see page 565) that this syndrome may, also, occur as an incomplete form, so called "forme fruste."

The study of the cases of brothers S. O. and N. O., however, leads us to doubt whether or not one of the outstanding symptoms of Werner's syndrome is correctly described by the term "scleroderma" or "poikiloscleroderma." To the best of our knowledge there is no case of true scleroderma described in the literature in which this disease occurs in families as a recessive familial disorder. Diffuse scleroderma usually involves the skin and tissue beneath the lower eyelid, the skin covering the nose and nostrils and the skin around the mouth and the chin. In most of these cases the skin of the neck, of the thorax and of the abdomen as well as the skin of the extremities is involved. In many cases of true scleroderma an intensive melanotic pigmentation is seen in some areas of the body, especially on the neck, in the axilla, on the trunk and buttocks. Areas of circumscribed hyperkeratosis, however, occurring on feet, insteps and elbows are not a feature of true scleroderma. In Werner's syndrome, in contrast to scleroderma, the skin changes begin with circumscribed areas of hyperkeratosis beneath the heels, beneath the large toes, on the lateral parts of the feet as well as on the instep and over the Achilles tendon. In Werner's syndrome areas of melanotic pigmentation are never observed. Scaling, however, along very fine, faintly yellowish brown stripes may be found in some cases. As a whole the skin in Werner's syndrome is white and waxy in color and has a reddish hue only on the parts of the extremities where it is exposed to pressure from clothes and shoes. These distinct differences in clinical features of true scleroderma and the "pseudo" scleroderma in Werner's syndrome are strikingly supported by the histological examination of the skin biopsies obtained from both brothers O. The histology of true scleroderma is characterized by edema, homogenization, fibrosis and sclerosis of the collagen fibers and obliterative changes in the vessels of the cutis. Lymphocytic infiltration of the subcutaneous tissue especially about the blood vessels is a characteristic histologic feature. These characteristics of true scleroderma are not found in the biopsies of our cases. In the histological examination of the skin biopsy of Sidney O. the horny layer seemed to be of normal thickness and structure. The pars papillaris was either somewhat flattened or definitely flattened. There was no homogenization or sclerosis of the connective tissue underlying the papillae nor homogenization of connective tissue of the pars reticularis. The hair follicles and the sweat glands were not numerous and, if present, were not well developed. No proliferative nor necrotizing arteritis was visible in the arteries of the subcutaneous tissue. The subcutaneous veins were more distended than usual. The elastic fibers of the corium were loose and appeared essentially unaltered. Fat cells were almost absent in the subcutaneous tissue.

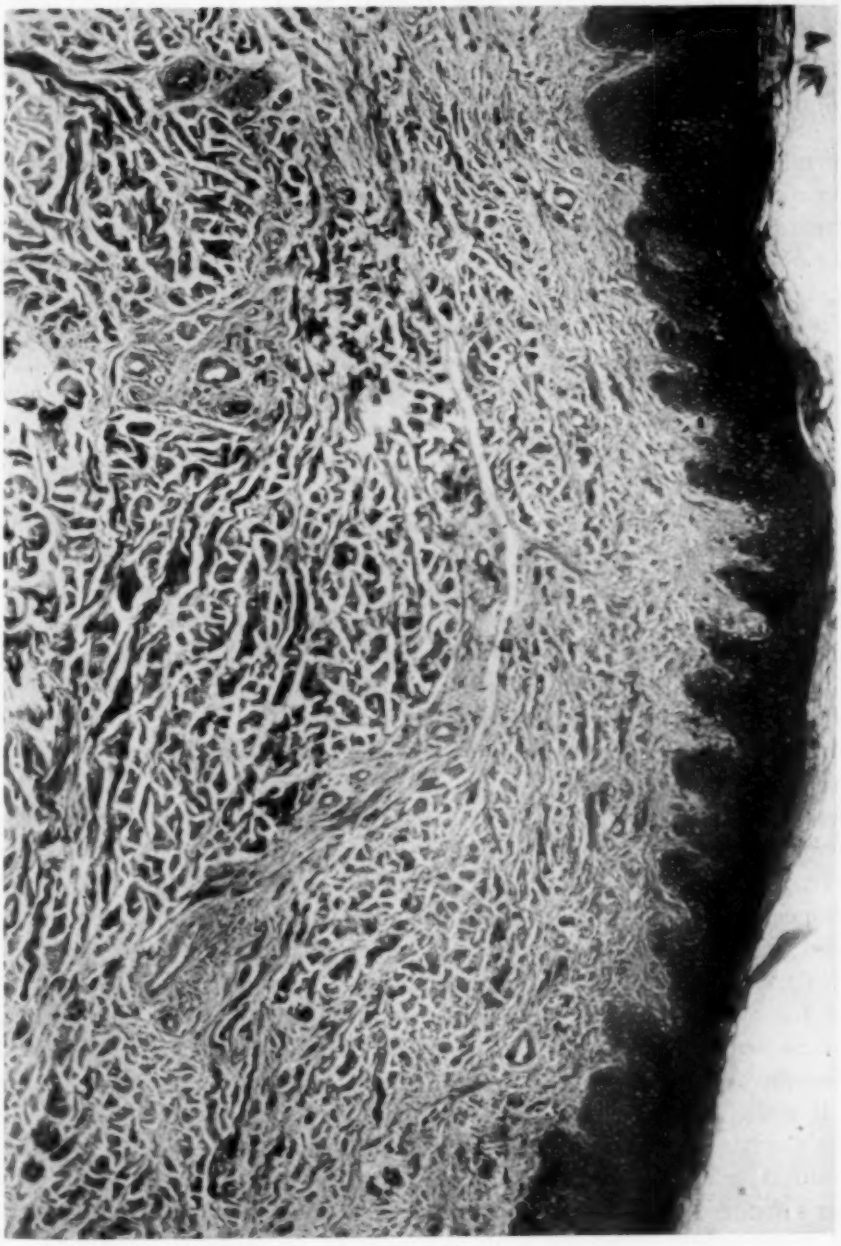


FIG. 16. Skin biopsy of Sidney O. Papillae fairly well preserved; subcutaneous tissue normal; no proliferative necrotizing arteritis visible.

We are indebted to Dr. H. Montgomery, of the Mayo Clinic, Section on Dermatology, for examination of our slides of S. O. He was kind enough to give the following opinion: "I would guess that the biopsy and slides of Sidney O. (N. 6018) were taken from the leg, probably the lower part of the leg, because of the large varicose veins present in the subcutaneous tissue. Some atrophy of the hair follicles is present, but this often occurs in skin taken from the legs and areas where the skin has been subject to friction, as from socks and garters. There is no evidence of so called senile skin, such as tinctorial changes in the staining of the collagen or basophilic staining of the elastic tissue, which can be seen in polychrome methylene-blue and hematoxylin-eosin stained sections. The slides of the skin show practically no inflammatory reaction, no appreciable obliterative changes in any of the vessels. The connective tissue fibers appear essentially normal and there is no decrease in thickness of the cutis. All this speaks against scleroderma.

"Pseudosclerodermatous infiltrations with ulceration, especially in the vicinity of the ankles, and poikiloderma-like changes are often seen in the relatively rare skin condition known as 'acrodermatitis chronica atrophicans.' Clinically, however, there usually is no systemic disturbance or evidence of systemic disease, and, histopathologically there is a rather specific picture with marked atrophy of the epidermis and flattening of the rete ridges with partial to almost complete loss of the cutis, the cutis being replaced by a dense infiltrate that is separated from the epidermis by a normal 'grenz' or border zone. Unless the sections were taken from a pseudosclerodermatous area one can rule out acrodermatitis chronica atrophicans on the basis of these sections."

The skin biopsy taken from Nathan O. showed more flattening of the pars papillaris than that of his brother Sidney. The histological pattern, however, was the same as described in the slides of Sidney O. Here, also, the connective tissue of the pars reticularis was not homogenized or sclerosed. There was no inflammatory reaction in the rete. A few lymphocytes were occasionally found around some blood vessels. In sections stained for elastic tissue no abnormal conditions were found either in the case of Sidney or Nathan O. The *muscle biopsies* taken from Sidney O. and Nathan O. showed no cellular infiltration or specific changes.

It is evident from these histological findings that the skin changes in Werner's syndrome are not identical with the skin changes found in diffuse or localized scleroderma. Such a classification of the skin disorder in Werner's syndrome is not justified since neither the clinical picture nor histological examination coincides with scleroderma or poikilosclerodermа. It seems more appropriate to designate the skin lesions in Werner's syndrome by a simple descriptive name such as "heredofamilial atrophic dermatosis with skin ulcers."

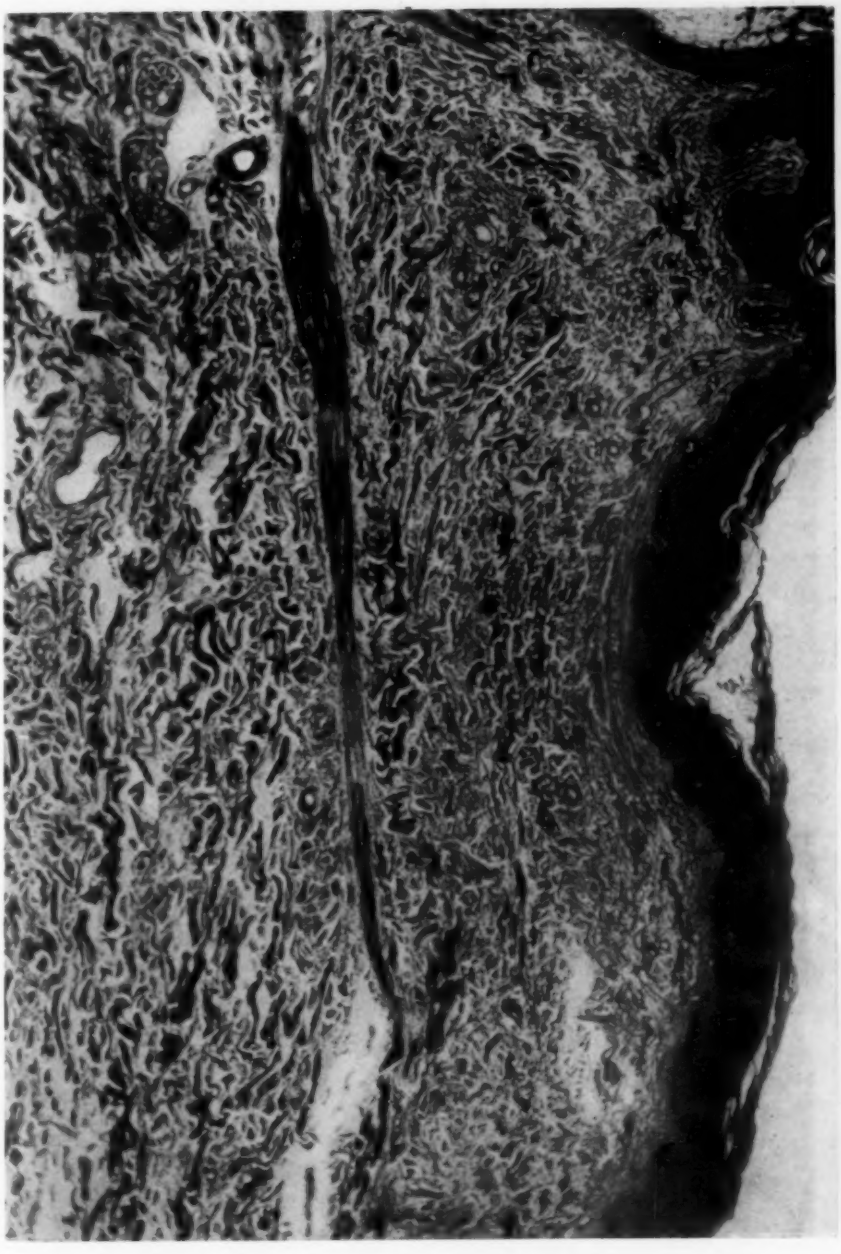


FIG. 17. Skin biopsy of Nathan O. Papillae are definitely flattened; subcutaneous tissue not homogenized; some veins distended. No inflammatory infiltration of arteries or tissues.

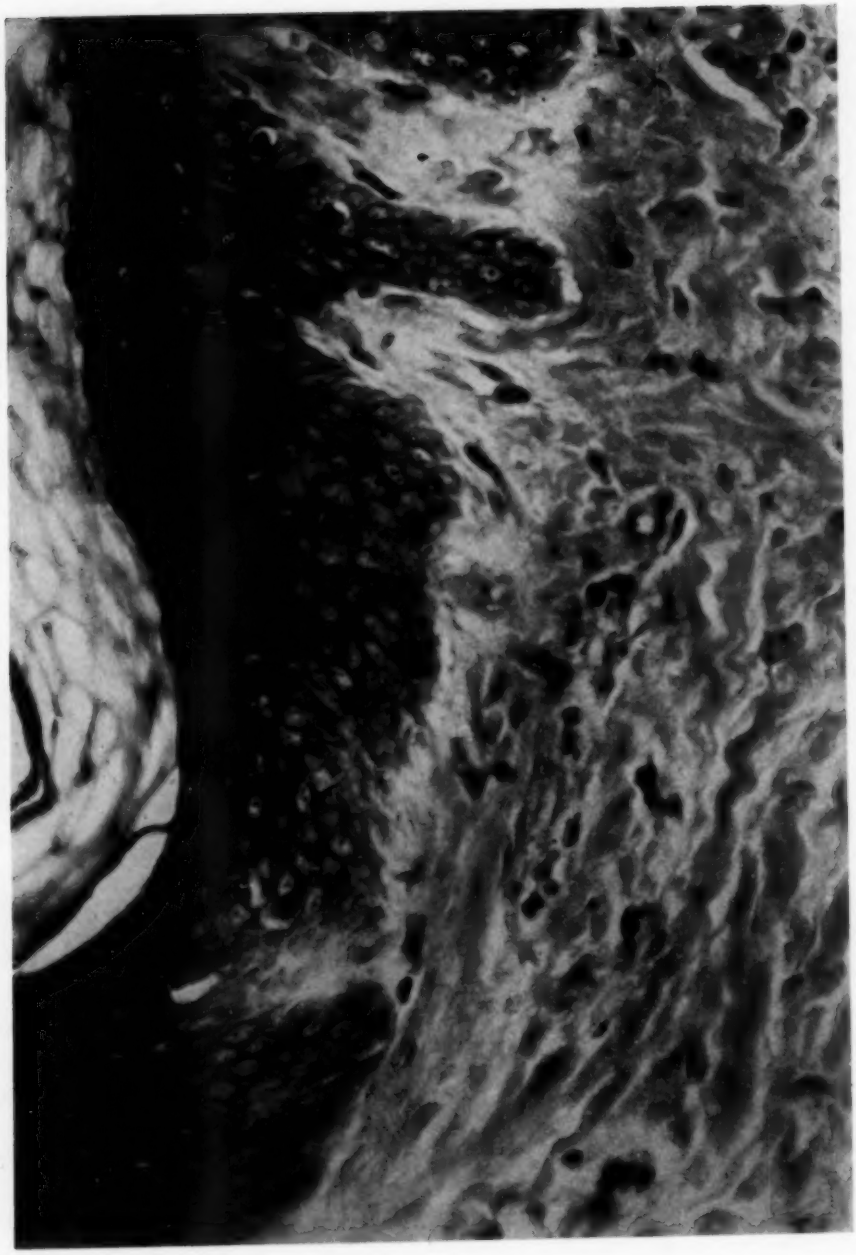


FIG. 18. Higher magnification of figure 17.

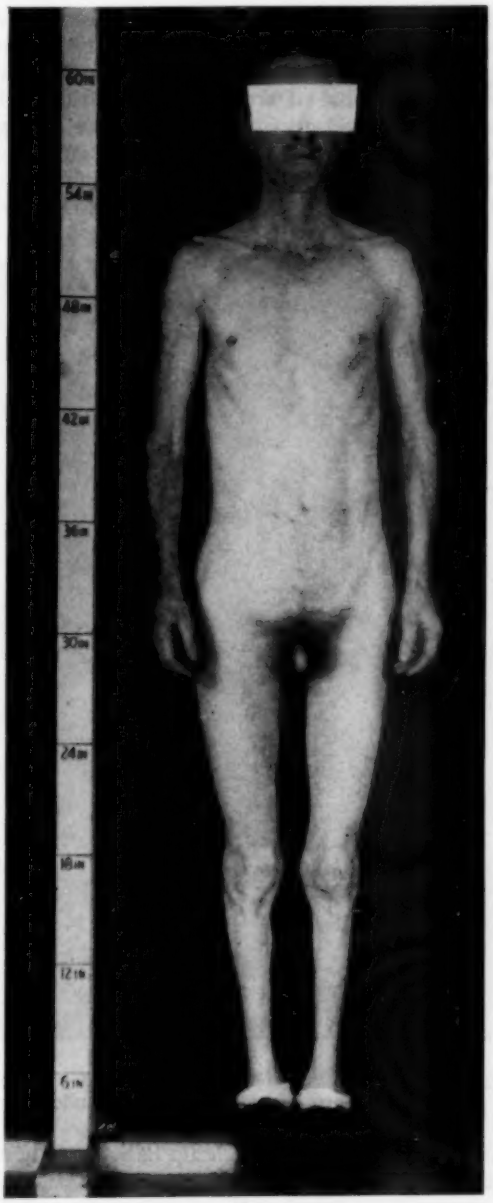


FIG. 19. George St. General leanness, extremely thin legs and arms.

Case 3. George W. St., 39 years old, was studied on the Medical Service of the Massachusetts General Hospital.* Mother and father were direct cousins. Both

* Dr. Fuller Albright was invited to see Sidney O. in our hospital in consultation. He remembered at once that he had observed a similar case. I am very much indebted to him for letting me examine this patient, George St., and include his case history in this paper.

were normal. He had two married sisters, 46 years old and 40 years old. The older sister had two healthy boys in the Navy. The younger sister had a healthy girl, 17 years of age. The patient was born a normal child but was delicate. He graduated from high school and from a school of architectural drafting. *Appearance:* He was short in stature—five feet. He had grown very little since the age of nine. Weight was 75 pounds. His maximum weight was 100 pounds, at the age of 22, when he entered the Navy, but at the time of his discharge he weighed 85 pounds. He looked older than his actual age. He did not know when his hair started to turn gray. At

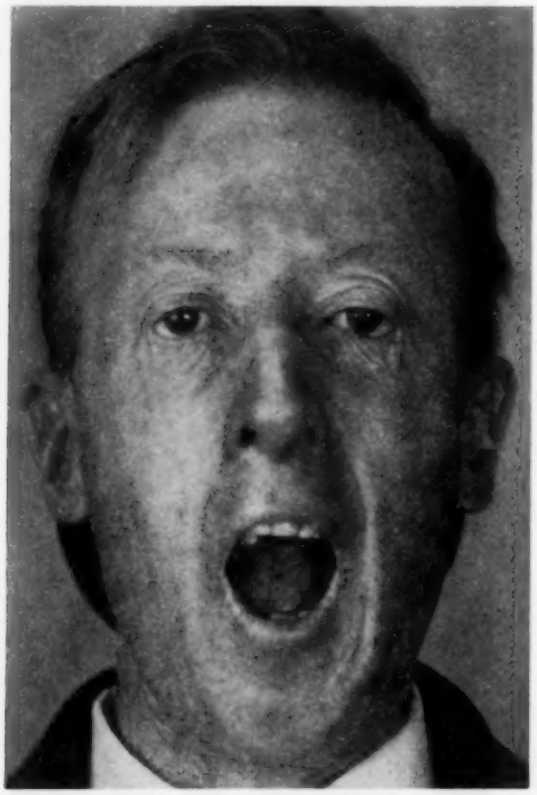


FIG. 20. Skin under lower eyelids wrinkled (in contrast to scleroderma). Aperture of mouth small. Hairs are fine and gray. Presenile appearance.

the age of 33 he was completely gray. The scalp hairs were now scarce, fine, and of an indefinite grayish color. His eyebrows were normal. He had only a few eyelashes. He shaved about twice a week. His beard was gray. His body hairs were almost absent. His pubic hairs were scarce and straight, not curled. The *skin* of his face was taut, but movable over the underlying structures. The nasolabial folds were distinct and formed taut, longitudinal lines. The aperture of his mouth was small but the opening of the mouth was not hampered. The skin of his neck and thorax was thin, transparent and movable. The skin of his upper arms and lower legs was taut and tightly stretched over the underlying tissue. The skin above the knees and elbows was normal. Although the skin on the dorsal parts of his hands was pliable, the skin over both ankles and both feet was so tightly pulled over the

bones that motion of both ankle, metatarsophalangeal, and phalangeal joints was limited. He walked with stiff ankle joints and everted feet.

Skin biopsy: "There is slight superficial keratosis. The rete pegs have disappeared. The pars papillaris is flat. The zone of prickle cells is reduced. No inflammatory changes of the subcutaneous tissue are seen. There is no cellular infiltration around or within the arteries. The walls of the arterioles are somewhat thickened. The subcutaneous tissue is loose. Neither homogenization nor sclerosis of the subcutaneous tissue is seen. The subcutaneous fat is very scarce. Some veins of the subcutaneous tissue are distended. The elastic fibers are essentially unaltered.

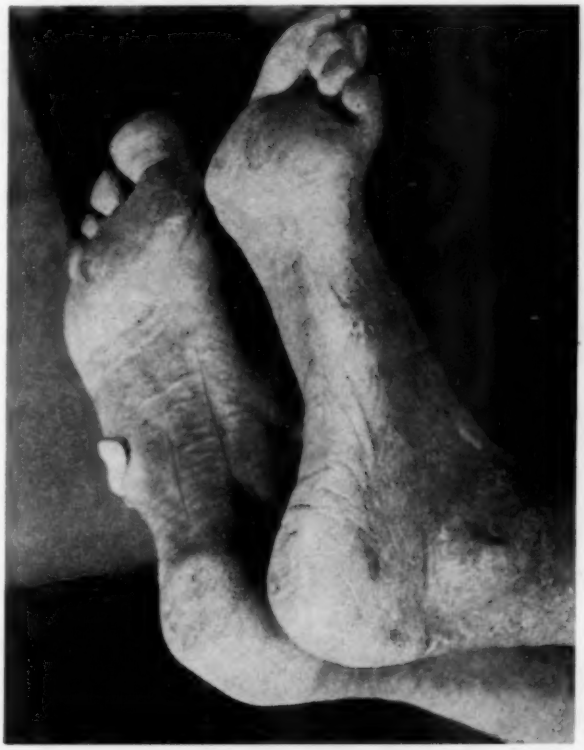


FIG. 21. Skin over both ankles tightly pulled; motion in ankle-joints impaired. Ulcers on left malleolus and sides of feet. Areas of hyperkeratosis.

Hairs and sebaceous glands are almost absent in this section." Areas of *hyperkeratosis* on his feet were the first signs of skin changes the patient had noticed. He reported that at the age of 17 he became aware of calluses on both soles under the large toes and both heels. No ulcers were present at this time. The first *ulcers* developed at the age of 37 on the lateral parts of both feet. He now had circumscribed areas of hyperkeratosis under both large toes, under both heels, and on the lateral margins of his feet. The ulcers were almost healed but the scars of former ulcers were visible on both feet. The *subcutaneous fat tissue,* as well as the *muscles* of upper arms, hands, lower legs and feet, were underdeveloped. The lower parts of arms and legs were so thin that they had a skeleton-like appearance. Circumference above the wrists was 13 cm.; above the ankle joints it was 15 cm. Hands and feet were very small in size. The fingers seemed somewhat deformed because the interphalan-

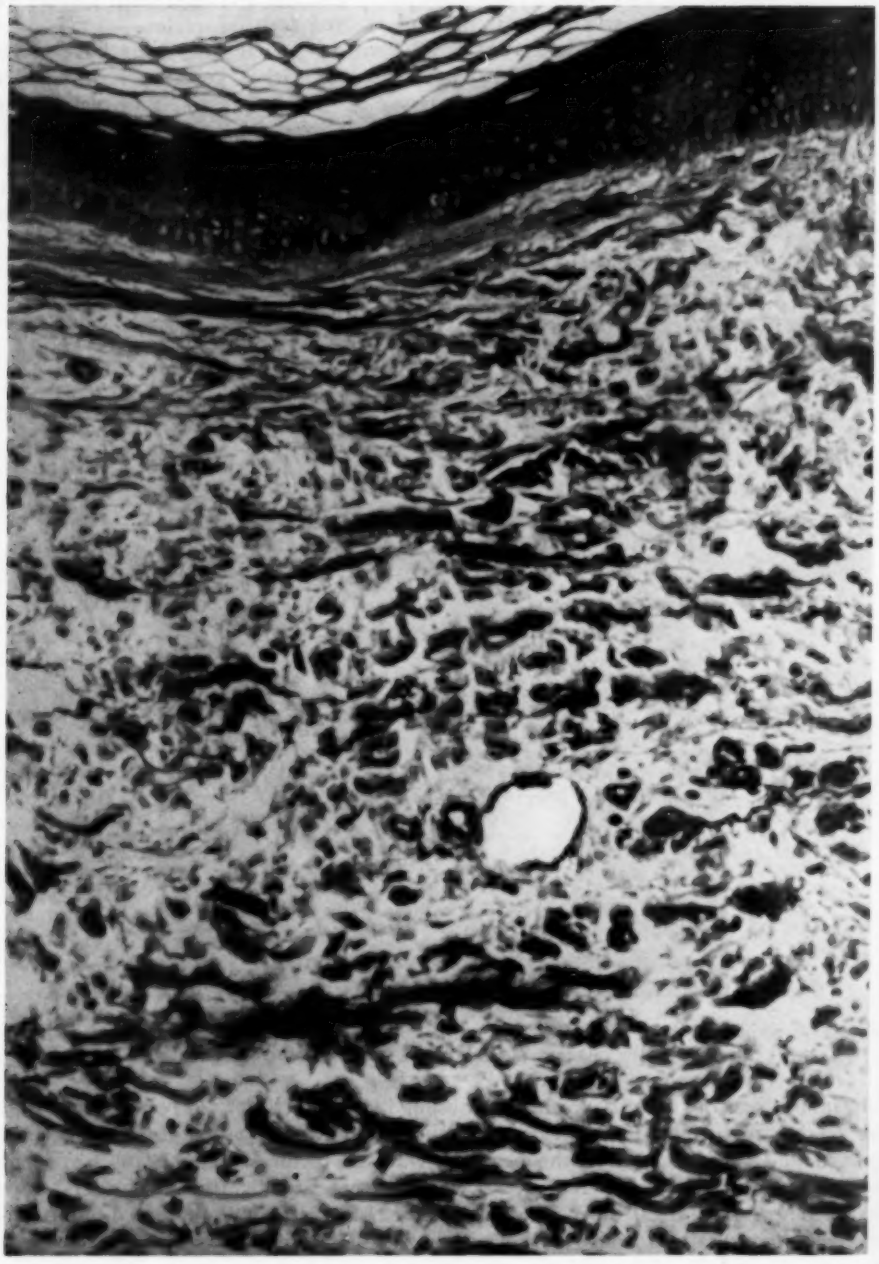


FIG. 22. Skin biopsy of George St. Papillae are entirely flattened. Small mucous layer. Prickle-cells reduced in number. Subcutaneous tissue normal; not homogenized. No inflammatory infiltration around arteries or in subcutaneous tissues. Some distended veins.

FIG. 23. Higher magnification of figure 22.

geal *joints* were prominent, as in an arthritic person. The roentgenograms of the bones in the parts where the dermatosis of the skin was evident showed *osteoporosis* due to decalcification. In the roentgenograms made at the Massachusetts General Hospital, November 30, 1941, small areas of calcium deposits were seen in the soft tissue close to the right fifth metacarpal phalangeal joint and of the proximal phalanx of the fourth right finger. Similar areas of calcium deposits were also seen around both ankles. At present calcification was noted only in the Achilles tendon. Calcification of the arteries was not visible in the roentgenograms of both lower legs. *Eyes:* At the age of 30 *cataracts* developed in both lenses. The cataracts were successfully extracted at the age of 34 by Dr. Chandler of the Massachusetts General Hospital. Both eyes were now aphacic and showed scars of a healed iridocyclitis. There was no proptosis of the eyes. The *nose* was fine in contour and somewhat elongated. The *chin* was small but not retracted. The *ears* were small and flat but did not protrude laterally from the head. The *voice* was high pitched and hoarse. The *teeth* were all developed but carious. The roentgenogram of the *lungs* showed thickening of the apical pleura on the right side. *Vascular system:* The heart was normal. Blood pressure was 130 mm. Hg systolic and 80 mm. diastolic. There was no visible arteriosclerosis. Electrocardiogram was normal. The reflexes were normal. A myotonic reaction could not be elicited. *Endocrine features:* The shortness of stature and the senile appearance with graying of the scalp hairs has already been discussed. The thyroid was not palpated. Basal metabolic rate in 1941 was − 14; in 1943, − 32. The sexual organs were very small. The penis was short. The scrotum was small in size. The testes, although descended, were of the size of those of a 12 year old boy. In 1941 the 17-ketosteroids in the 24 hour urine were 13.3 mg.; in 1943, 5.7 mg. The sella turcica, on roentgen-ray examination was normal. *Laboratory findings:* Total serum protein, sodium and potassium and calcium determination in the serum were normal.

Comment. This patient was the child of first cousins, but as far as could be ascertained there was no similar case in his ancestry. The features of Werner's syndrome present in George St. were: Presenile appearance, shortness of stature, canities, skin changes consisting of stretching of the taut skin over the underlying structures on the lower legs and feet, skin ulcers, areas of hyperkeratosis, atrophy of subcutaneous tissue as well as muscles of the upper arms and lower legs, hands and feet; small chin, hands and feet; osteoporosis; sexual underdevelopment. Although potential diabetes and arteriosclerosis were not evident in this case the other features are convincing that this case belongs to the group of Werner's syndrome. In 1941 our patient underwent a lumbar sympathectomy because it was thought that the skin changes were due to scleroderma and the ulcers were due to trophic disturbances of the skin. A follow-up note of the Massachusetts General Hospital, in the case history, reads as follows: "I cannot see that any benefit was obtained from this operation. Since that time his condition has remained essentially unchanged." It seems, therefore, that the ulcers are not the result of a trophic disorder. The good healing of the ulcers after grafting, in the case of Sidney O., supports the opinion that the ulcers are due to the vulnerability of the atrophic and stretched skin to outside pressure from shoes and clothes. The gross skin changes are the same as in all cases reported. The histological examination of the skin biopsy concurred with the biopsies of the

brothers Sidney and Nathan O. in that the characteristics of true scleroderma were not found. Homogenization and sclerosis of the subcutaneous tissue as well as inflammatory reactions consisting of lymphocytic infiltration in the subcutaneous tissue and proliferative arteritis were absent. These negative findings on three patients with Werner's syndrome demonstrate that the taut and stretched skin is not the result of true scleroderma but rather a part of the general abiotrophic process which involved the endocrine glands as well as the whole body. It is highly suggestive that such an abiotrophic degenerative process which manifests itself in the second and third decades of life may originate in a recessively transmitted hereditary defect of the germ plasm.

Case 4. Miss M. F., 29 years old. There was no history of intermarriage in her ancestry. No similar cases were known in the family. The family was highly intellectual. Father and brother were outstanding professors in medical schools in Germany. A maternal uncle was one of the great physiologists of the past century. The girl was mentally retarded, having the mentality of a 12 year old child. She graduated, however, from a private school. Her appetite became very poor at the age of 17. Instead of eating her meals she hid her food and threw it away when she was unobserved. *Appearance:* She was very short in *stature* and considerably underweight. She looked like an old woman, about 20 years older than her actual age. The scalp hairs began to turn gray around the age of 20. They were sparse, fine and of an indefinite grayish color. The eyebrows as well as the eyelashes were scarce. The axillary hairs were completely absent. Only a few short pubic hairs were found. The *skin* of the face was wrinkled, but taut. Longitudinal firm naso-labial fat gave the face an old appearance. The skin on the chest and abdomen was thin and atrophic. No pigmentation or telangiectases were present. The skin of the upper arms and hands was atrophic and thin. Over both hands the skin was pliable like tissue paper. In contrast to the skin on the forearms and hands the skin over both lower legs was taut and adherent to the underlying structures, the latter especially noticeable over the ankles and the insteps. The motion in the ankle joints was moderately impaired by the stretched skin, and she walked with everted feet. She complained of pain in circumscribed areas of *hyperkeratosis* under both large toes, both heels and on the external sides of the feet. She reported that she had *ulcers* on the lateral malleolus and on the instep from pressure of her shoes. The ulcers healed only after a long time. Ulcer scars, but not active skin ulcers, were visible. *Nails* on hands and feet were poorly developed, but all were present. The subcutaneous fat tissue and the muscles on both lower legs and upper arms were thin and poorly developed. The lower legs had a skeleton-like appearance. Roentgenograms of the bones were not made. The phalangeal joints on both hands had the appearance of arthritic joints with thickened periarticular tissue. The patient did not complain of pain in her joints. At the age of 24 she noticed difficulty in reading. Beginning *cataracts* were found. At the time she was observed, at 29, the cataracts had almost matured. Her *nose* and *chin* were small. The *ears* were small and flat, but did not protrude laterally from the head. The *voice* was high pitched and slightly hoarse. The *lungs* were normal. The *heart* was normal in size. Blood pressure was 130 mm. Hg systolic and 90 mm. diastolic. There was no note in regard to the arteries. *Endocrine features:* Senile appearance, canities, and the very short stature have already been described. The thyroid was not enlarged. No proptosis of the eyes was noticed. Basal metabolic rate was not recorded. The patient first menstruated at the age of 16. After that menstruation was sparse, occurring only a few times during the year

and ceased at the age of 25. Gynecological examination reported by a gynecologist (Dr. Weber): "External genitalia normal; hymen intact. By rectal examination neither uterus nor ovaries could be felt distinctly; probably underdeveloped." No records of laboratory examinations were available.

Comment. The patient was seen almost every year, from the age of 29 to 37. The cataracts were operated upon at the age of 31. At the time she was under observation I did not make the diagnosis of Werner's syndrome because I was then not aware that such a syndrome had been described. Since in later years I have become familiar with the literature there is no doubt that the features of this patient, i.e., short stature, canities, cataracts, atrophic dermatosis with taut and stretched skin, sexual underdevelopment, justify in retrospect the diagnosis of Werner's syndrome. Stunted growth resulting in short stature and sexual underdevelopment was reported by R. F. Varney, A. T. Kenyon and F. S. Koch[17] and by F. Albright, P. H. Smith and R. Fraser.[18] L. Wilkins and W. Fleischmann[19] designated this syndrome as "ovarian agenesis" because they demonstrated in their cases, by their histological studies, that the ovaries did not develop. Wilkins and Fleischmann suggest that ovarian agenesis as well as stunted growth is due to defects of the germ plasm and not to endocrine deficiencies of normally developed organs. "It is well recognized that multiple germinal defects frequently occur in the same individual." We are inclined to explain Werner's syndrome as the result of multiple germinal defects because it presents recessive characteristics and is of heredofamilial occurrence and because its endocrine manifestations, namely stunted growth and sexual underdevelopment, are only a part of its multiple features. Wilkins and Fleischmann tabulate 32 cases published by different authors in which they suggest the presence of ovarian agenesis. Only one of these cases (case 10 by F. Albright, P. H. Smith, R. Fraser[18]) exhibited progeria and cataracts in addition to ovarian agenesis. Although skin changes and heredity are not reported, it seems possible that this case is related to the group of Werner's syndrome. When in the future we have better learned how to differentiate the features of functional endocrine deficiencies from the endocrine features resulting from germinal defects, reports of Werner's syndrome and related syndromes will become more numerous.

II. Rothmund's Syndrome

August Rothmund,[20] in a paper entitled "Cataracts in Association with a Peculiar Degeneration of the Skin" in the Archives der Ophthalmologie, 1868, writes as follows: "A boy five years of age was brought to the ophthalmological clinic in Munich who suffered from a cataract of one eye which was not due to a trauma, and gradually developed during a couple of weeks. I noticed there was already at this time a peculiar marmorization of the skin of this boy. To my surprise two other children living in the same vicinity and also suffering from cataract and peculiar skin

degenerations came into the clinic. My attention was even more attracted by the report of the parents of the children claiming that several such blind children exhibiting the same skin changes were living in the same section of the country. Experienced dermatologists (colleagues of the medical faculty of the University of Munich) to whom I demonstrated the cases, assured me that they never had seen a similar skin disorder. For this reason I decided to explore the situation in loco and to visit the 'Kleine Walsertal' during the fall vacation. The 'Kleine Walsertal' in the Austrian Bregenzerwald in Vorarlberg, is a small dead-end valley surrounded by high mountains of the Alps, which could be reached only by a small pass road from the Bavarian Allgäu mountains. In this valley are located only three little villages, Ritzlern, Hirscheck and Mittelberg with altogether 1500 inhabitants." Almost all the families of this valley are related, and intermarriage in the same family is not infrequent. Rothmund found in each of these three villages one family, the children of whom exhibited cataracts resulting in blindness and simultaneously occurring skin alterations.

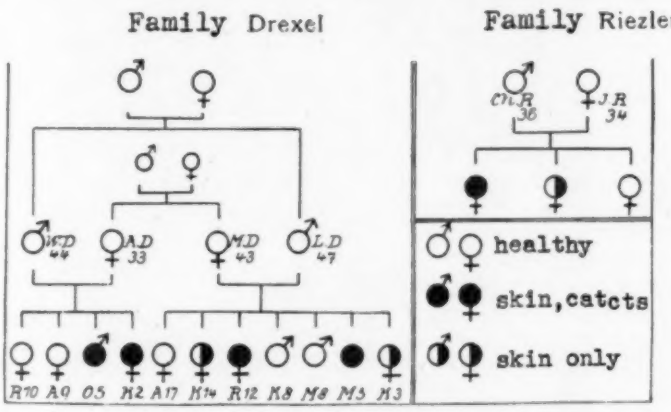


FIG. 24. Family tree of the Drexels and Riezlers.

The three families involved were: (1) Family Wolfgang Drexel in Mittelberg. There were four children. The two older ones (10 and seven years old) both females, were normal. The two younger ones, a boy, Oswald, five years old, and a girl, Katherine, two years old, it was noted, had skin changes at the age of six months and cataracts at the age of five. (2) Family Lukas Drexel in Hirscheck. There were seven children. The oldest, a female of 17, was normal; the second, a female, Karolina, 14, had slight skin changes but no cataracts; the third, a female, Rosamunde, 12, exhibited skin changes at three months and developed cataracts at six. The fourth and fifth were male twins, eight years old, and normal. The sixth, a female, Maria Katharina, five years old, developed skin changes at the age of three months and cataracts at the age of four. The seventh, a female, Maria Karethina, three years old, also developed skin changes at the age of three months, but the eyes were still normal. (3) Family Riezler, in Ritzlern, had three female children. The oldest, Rosamunde, four years old, developed skin changes within three months of birth, and beginning cataracts at the age of four years. The second child, Therese, three years old, developed skin changes within three months of birth. Beginning cataracts were

found at the age of three years. The third child, also a female, five years old, did not then show signs of skin abnormalities or cataracts.

Only one *grandmother* of one of these families had a similar skin anomaly, but was not blind. No other ancestor was afflicted with a similar abnormality. Rothmund reported that all these children were similar in their general *appearance*. The children were physically and mentally normal in development. Other than the eyes and skin all organs were found normal. Urine contained no sugar or other abnormal

FIG. 25. Rosamunde R. (Reproduced from paper by Rothmund.) Telangiectases, corresponding to livedo reticularis, surround scaling white skin.

constituent. The *cataracts* formed from the age of four to six. They developed rapidly in both eyes, never unilaterally. The cataracts started as star-like opacities at the lower posterior pole of the lens and extended, in a short time, toward the center of the lens, resulting in blindness. The *skin changes* were not present at birth. Marmorization of the skin became visible first in the face, three months after birth. Later the skin on the knees, on the ears, on the buttocks and on the extremities—first the extensor, later the flexor surfaces—became involved. Only the vola manus and the bends of the elbows and knees remained free. In the first stages the skin

changes corresponded to the livedo reticularis, later striae and round reddish spots appeared. The striae were not prominent over the surface of the skin but were more or less beneath the surface. With the naked eye the surface of the skin looked level and no prominences were visible. Applying pressure with the finger upon the skin the reddish color disappeared but a light yellowish-brown color remained. The reddish color of the lesion after scaling became brown-red and yellowish and finally appeared as a firm colorless scar. The skin then had an areolated appearance resulting from the normal skin being encircled by these yellowish or colorless scars. The process described went on continuously but slowly, with the result that red lines, like telangiectases, and scar tissue were present at the same time. Neither itching, vesiculations, ulcers nor crusts were present. The areas of the skin now involved were extremely fine, soft, white and transparent so that the veins beneath the skin were visible to their smallest ramifications.

The *histological examination* performed in 1868 is inconclusive when compared with present-day methods. Staining methods with aniline dyes had not been developed. A piece of superficially unaltered skin and a piece corresponding to one of the reddish striae were examined. The normal skin of the patient showed the same picture as normal skin does, but in the corium layer the number of elastic fibers seemed less than in a normal skin. The horny layer of the pathologically changed piece of the skin was not undulated but flat and not transparent. The mucous layer showed the same condition, but the changes were more marked in the center of the red striae and less in its periphery. The mucous layer was not well defined towards the reticular part of the corium and rested plainly upon it. The pars papillaris was lacking and was replaced by a layer that showed no definite structure. It contained some blood vessels and clumps of hemoglobin derivatives. In separating the mucous layer from the underlying tissue neither indentations nor elevations resulted. Fat droplets were visible between the two layers. The transition of the layer replacing the pars papillaris into the subcutaneous tissue was not clearly defined. The subcutaneous tissue did not show remarkable changes. It was composed of fat droplets, perhaps of fewer hair follicles than normal, some of them not containing hairs, of some coil glands and connective tissue. The elastic fibers were not compressed. Rather loose fascicles surrounded alveolar spaces filled with tissue of the same undefined nature as the one replacing the pars papillaris. Rothmund summarized the results of his examination as follows: "The essential finding of the examination of the diseased piece of skin was the fatty degeneration of the rete Malpighii and the disappearance of the pars papillaris." Concerning the etiology of the disease Rothmund suggests a heredofamilial disorder of the ectodermal layer as the lens is also derived from a bulge of the ectoderm.

Comment. Designating these skin changes according to the nomenclature of the time as "Parenchymatous inflammation" Rothmund hesitated to give the syndrome a special name since he could not find a description of a similar skin alteration combined with simultaneous formation of cataracts. Skin changes similarly observed in adults were later described in the dermatological literature as "Atrophia Maculosa et Striata." According to *Ormsby and Montgomery*[21] such lesions are also observed as a congenital atrophy. These authors believed that the skin changes in the congenital cases are a congenital defect rather than an acquired atrophy. The case of *Riehl and Vörner*[22] (1903) may be due to a congenital defect and belong to this group. The skin lesions of the children observed by Rothmund were certainly not congenital since they appeared three to six months after birth.

The fate of these children was reinvestigated 67 years after Rothmund's original publication by R. Seefelder (1934). The two children of Wolfgang Drexel had died. Oswald D. died at the age of 56 and Maria Katharine D. at 40. Oswald had married but had no children. Maria Katharina remained single. Photographs taken of Oswald at the age of 40 showed no skin changes. The scalp hair was ample and apparently not gray, but the face was without mustache or hairs. There were no remarks concerning the height or other physical characteristics which may have developed in later years. The investigation concerning the family of Lucas Drexel was more successful. Karolina, in whom only skin changes were noted, was living at the age of 83. She had 13 children. Only one daughter had her eyes operated upon at the age of 48. Four children died as infants; nine children were alive and healthy. The skin on both arms of this 83 year old woman was thin, resembling tissue paper. Round areas of dark brown pigmentation were observed on both arms. The scalp hairs, even at that age, were relatively well preserved. Her sister, Rosamunde, who had cataracts and skin changes as an infant, was living and aged 76. No report concerning her skin and hair was made. She had not married. The third sister, Maria Katharina, died at the age of 70. She had married but had no children. Maria Karethina, the fourth sister, was alive at the age of 72. Her height was 150 cm. (four feet). Her hands and feet were very small and her fingers and toes were short. The size of the hands was that of a 10 year old child. The extremities were very short. The skin over face and forehead showed a network of dark wine-red striae. The skin between the reddish network was yellowish. The skin on the extremities showed no red striae but was thin, like tissue paper, and diffusely pigmented with round areas of darker brownish pigmentation. The scalp hairs had almost completely disappeared at the age of 40. It was especially remarkable that the old woman was mentally very alert, talkative and full of humor.

Concerning the fate of the children of the third family, that of Peter Riezler, no details are known. Seefelder, however, added a report of another member of the family Riezler, who was the product of the intercourse of father and daughter. Peter Riezler, 30 years old, had red striae on his face, round pigmented spots on both arms and hands. He had cataracts in both eyes. His height was 146 cm. (below four feet). His mental development was retarded.

The follow-up study of the three families demonstrated that the children originally described lived to an average age or even to an old age. The patients who exhibited cataracts as children, as well as skin changes, did not marry and had no children. Only Rosamunde, who had only slight skin changes, but no cataracts, had 13 children. The other brother and sisters who did not develop cataracts or skin changes, if married, had healthy children. Only one of the original children reported by Rothmund (Maria Karethina Drexel) remained short in stature, had short extremities, small hands and feet and became gray and bald at the age of 40.

A. Nieden[23] in 1887 described a girl 22 years old who at the age of 15 noticed telangiectases on her face. Small red areas of pea or pin point size developed on the forehead, cheeks and upper part of the neck. Such lesions later appeared as well on the hands and extensor surfaces of the arms. Cataracts formed on the posterior poles of the lenses at the age of 20. Menstruation started late, at 15, and was irregular. "The slim, lymphatic appearance of the girl was striking at the first glance." No other features were reported. Although the occurrence of a similar disease had not been recorded in her family, this case probably belongs to Rothmund's syndrome.

Under the title "Télangiectasie généralisée et cataracte congénitale" *F. Terrien and Prélat*[24] (1909) reported the case of a six year old girl. Three brothers died during infancy of bronchial pneumonia, complicating measles; no skin changes were present in the case of these infants nor in the case of the parents. It is reported that the child, herself, at the age of three months, already exhibited areas of telangiectasis of the face, the buttocks, and the skin of the extremities, especially on the extensor surfaces. Small areas of brownish net-like pigmentation accompanied the areas of telangiectasis. In addition to these features a thickening of the skin resembling myxedema was noted. The hairs of the scalp were normally developed; however, the eyebrows were very sparse. At the age of six the child had cataracts in both eyes, the first appearance of which was not reported. Although the authors suggested a thyroid deficiency as the cause of the disorder (no data were given concerning the condition of the thyroid), there is no doubt that this case belongs to Rothmund's syndrome. This is evident from the type of the skin lesions as well as from the early development of the cataracts.

Zinsser,[25] in 1910, described two brothers under the title "Atrophia cutis reticularis cum pigmentatione." *V. Janovsky*,[26] in 1921, under the title "Three cases of familial skin atrophy (Poikiloderma atrophicans)" reported three sisters who exhibited skin changes on the cheeks corresponding to the livedo reticularis, with redness in honeycomb configuration, central skin atrophy under scaling and pigmentation. The children reported by Zinsser also had lesions on both hands. These children, however, did not have cataracts. Since formes frustes (incomplete syndromes) were reported in the children of Rothmund's original description (Karolina D. had only skin changes but no cataracts) it seems possible that these children, also, are abortive cases of Rothmund's syndrome.

A. Siegrist,[27] in his book "Der graue Altersstar," reported the case of a four and a half year old girl who developed cataracts at the age of six months. The skin changes reproduced from a colored design (figure 19 of the book) were of the same kind as described by Rothmund.

A. F. Schnyder[28] added to the case of A. Siegrist the complete history and description of the case of the younger brother of the patient already reported by A. Siegrist. The child was the youngest of four sisters and brothers. The oldest girl was the patient reported by Siegrist. The two others were healthy. There was no report concerning the intellectual ability of the parents. The boy, five years old, rapidly developed bilateral *cataracts*. *Skin* changes had been observed at the age of five months. They developed first on the face as net-like telangiectases, later as pink-reddish striae, which resulted in round areas and stripes of skin atrophy. Pigmented and hyperpigmented areas intermingled with telangiectases were seen on the skin of cheeks and ears. The extensor surfaces were more involved than the flexor surfaces of the extremities. The bend of the elbows and knees was free as were the soles and the vola manus. The diseased parts of the skin were dry, scaling and tender. No ulcers or crusts resulting from exudations were seen. The involved areas resembled lesions occurring after an overdose of roentgen-ray therapy. The *hands* were short and clumsy. The body was otherwise well proportioned. The scalp *hair* was sparse and fine, light blonde but not gray. The hairline on the forehead and neck was higher

than normal. *Endocrine features:* The thyroid was normal. Sella turcica was normal. The right testis was entirely absent; the left testis was pea-sized and not descended.

Comment. There is no doubt that sister and brother, the sister described in 1928 by Siegrist, and the brother described in 1934 by A. F. Schnyder, exhibit Rothmund's syndrome in all its details of skin changes. It is of

FIG. 26. Case of a peddler. (Reproduced from paper by B. Bloch, H. Stauffer.) Appearance presenile. Thin arms in contrast to globulous abdomen. Very short hands. Skin of face, abdomen, and extensor surfaces of lower arms covered with telangiectases in net-like and round spot arrangement. Pendulant breasts. Genital organs underdeveloped.

interest that sexual retardation had been observed in the boy at the age of five. Canities was absent but the hair line of the boy was high in front and on the neck. The hands were short and the fingers clumsy, a feature not observed by Rothmund in his original description.

B. Bloch and H. Stauffer [29] in 1929 described three patients who belong to the syndrome under discussion. The title of their paper was "Skin diseases of endocrine origin, poikiloderma-like changes in connection with underdevelopment of the sex glands and dystrophia adiposogenitalis." The authors apparently were not acquainted

with Rothmund's or Werner's publications. The second case is of special interest because of the detailed description of the appearance, illustrated by photographs, as well as the histological examination of the skin by such a dermatological authority as B. Bloch. The patient was a 40 year old peddler, of short stature. In spite of a child-like face he looked old for his age. There was no hereditary history. At the age of four and a half years both eyes were operated upon for cataracts. As a child he was sickly. *Hair* was gray at 25 and sparse; the patient later was bald. There were no pubic hairs. This case was also presented by W. Lutz, Swiss Dermatological

FIG. 27. Knee. Round spots of telangiectases. Yellowish to dark pigmented areas, intermingled with white depigmented areas.

Congress, Basle, 1928. Obesity of chest and abdomen developed at 25. In contrast to the fat torso the extremities were strikingly thin, small and delicate and did not seem to fit the heavy torso. The *extremities* were too short, the fingers almost like stumps. *Muscles* and *subcutaneous fat* on the distal part of the extremities, in contrast to face and abdomen, were decidedly underdeveloped. The hands and feet were particularly small. The *skin* of the scalp was thin and tightly stretched. Numerous irregular *pigmented* as well as *depigmented* spots were distributed over scalp, face, and extremities. Areas of fine telangiectases were present in great numbers on the cheeks, the chin and the thorax. They gave these parts a faded red color. The *ears* were stunted, with only rudimentary lobes, and were covered with brown and white spots and numerous telangiectases. There were no eyebrows. The eyelashes were

represented only by an occasional hair. The face was devoid of hair. The *skin* of the trunk was scaling, dry and plainly atrophic. The veins could be seen through the atrophic skin. The atrophy was diffuse in some areas, in others more circumscribed. Telangiectases were present here as well as striae, especially below the umbilicus. The skin over the extremities, especially on the extensor surfaces, was changed in a similar manner, even more markedly than on the trunk. Areas of telangiectases were noted mainly on elbows and knees; yellowish to dark pigmented spots were intermingled with white depigmented areas. Numerous *hyperkeratotic* areas on wrist and palm, as well as on the soles, were present. The hyperkeratotic spots had peculiar hollows in their centers. Those of the feet resembled oyster shells. The *nails* on fingers and toes were markedly altered, partly missing, partly only horny scales remained. There were no hairs on the extremities. A few stunted, straight hairs were on the pubic region. *Endocrine features:* The voice was unchanged. Libido appeared at 16. External genitalia were underdeveloped. The patient was heterosexual, and had never had intercourse. The penis was infantile, 3 cm. long. The scrotum was the size of a walnut. Testicles as large as beans could be pushed back into the abdomen. Sella turcica was small. The thyroid was small; the left lobe showed a firm, smooth nodule about the size of a nut. According to the patient's statement only 30 teeth had developed. Some were rudimentary; the second incisors and the premolars were missing on both sides. Urine was normal. No blood sugar value was reported. Temperature was low, between 95° F. and 96° F. Pulse rate was normal. Reflexes were normal. Roentgenographic examination of *bones* showed atrophy (*osteoporosis*). The skull was thin, like that of a child. Definite arteriosclerosis was visible in the roentgenograms. *Histologic examination* of a biopsy specimen from a region above the right knee showed the following: "The horny layer was wider than normal throughout the entire section. The width of the epidermis was irregularly reduced; in some places only a few cell layers remained. Here the characteristic differentiation was no longer present. The basal cells were irregular and flattened, there was no spinous layer, and the boundary line between epidermis and cutis was straight. In other places the epidermis was broader, the differentiation of the layers was preserved, and the rete pegs and thin corresponding papillae were present but had an irregular form and arrangement. In the atrophic places the pigment was missing, whereas in others, especially in the brown spots, it was clearly increased. The sweat glands and follicles were entirely absent. The connective tissue of the cutis was unchanged. The elastic fibers were generally well developed, but in some papillae they were clumped, whereas in others only a few were present. In the papillae and in the pars reticularis there were greatly dilated capillaries. At one place in the wall of a blood vessel there was a deposit of lime."

Comment. The case is of special significance because it showed those features in an adult patient which were described by Rothmund in children. There is little doubt that one is justified in including B. Bloch and H. Stauffer's case in Rothmund's syndrome since the patient had cataracts at the age of four and a half and the skin changes also began at an early age. The skin exhibited the same characteristics with telangiectases, scaling, pigmentation and depigmentation, as described by Rothmund. His appearance was similar to Maria Karethina Drexel, described by Rothmund as a child and reported by Seefelder at the age of 70, in his follow-up study of Rothmund's cases. The absence of a familial history in Bloch and Stauffer's case is probably due to the fact that the patient had already left home when a child and had always been on the road as a peddler or beggar.

Histological examination of the skin biopsy with modern staining methods also confirmed the observations made with primitive methods by Rothmund, 62 years ago. B. Bloch and Stauffer apparently did not know of Rothmund's original description. In respect to the classification of the skin changes, the authors made the following important statement: "There were no marked inflammatory and no *scleroderma-like* or myxedema-like changes." "A classification with poikiloderma atrophicans vasculare which Jacobi first described would perhaps seem the most plausible. However, there are some objections to this; the telangiectases and, also, to some degree, the atrophy, are much too slight in comparison with typical cases. As can be seen in the photographs and models, the changes in the pigment here are (poikiloderma atrophicans vasculare, Jacobi [30]) of foremost importance and, in addition to the dry and atrophic consistency of the skin, are outstanding in the clinical picture. Moreover, as has been clearly shown in his detailed summary of the literature on this subject the term poikiloderma is not applied to a sharply defined pathologic entity, but rather a group of variable symptoms. It becomes evident, when one reads the literature on this subject, that different and dissimilar dermatoses have been grouped under this name only on account of their superficial resemblances. These diseases are even less an etiologic entity, so that the classification of an individual case in this group means little and does not aid us in regard to its pathogenesis. Our cases, also, differ from Jacobi's type in the high grade regressive changes of the hair, the nails, the follicular apparatus and the sweat glands."

B. Bloch and H. Stauffer in their attempt to connect poikiloderma atrophicans vasculare with primary endocrine disturbance collect and discuss cases in the literature in which poikiloderma was found together with endocrine symptoms. Cases reported by K. M. Bowmann and E. C. Clark,[31] L. Wertheim,[32] and R. Leginsky [33] are cited by Bloch and Stauffer as related to their own cases. The case published by L. Wertheim had a pituitary tumor and poikiloderma atrophicans vasculare. The skin changes started late in life. There were no cataracts present. The case of R. Leginsky had skin changes described as poikiloderma vasculare atrophicans, which also began late in life. No cataracts were present. This patient had a questionable atrophy of the pituitary gland. Both cases have in their history, in their general appearance and in their clinical symptoms very little in common with Bloch and Stauffer's patient. They do not belong to the group of Rothmund's syndrome. K. M. Bowmann and E. C. Clark's [31] patient, however, had diffuse atrophic skin changes, with telangiectases beginning in early life and involving the entire surface of the body; ulcers on hands and feet; amputation of some fingers and toes because of secondary infection; bilateral cataracts at the age of 38; sexual underdevelopment; early arteriosclerosis but no graying of the scalp hairs. The scalp hairs were abundant and dark. Basal metabolic rate was —14; blood sugar 87 mg. per 100 c.c.; tolerance curve flat. The patient died at the age of 39. At autopsy the endocrine glands did not show any abnormality. The

histology of the skin was thought to be similar to poikiloderma atrophicans vasculare. The negative findings on examination of the endocrine glands certainly did not show any relation of the skin changes to endocrine disease. For the question under discussion, however, it seems of interest to consider whether or not the case of Bowmann and Clark belongs to Rothmund's or to Werner's syndrome since he had cataracts, atrophic skin changes with telangiectases and sexual underdevelopment, early arteriosclerosis and skin ulcerations with spontaneous amputations of fingers and toes. In fact this unique case exhibited features of Werner's as well as Rothmund's syndrome.

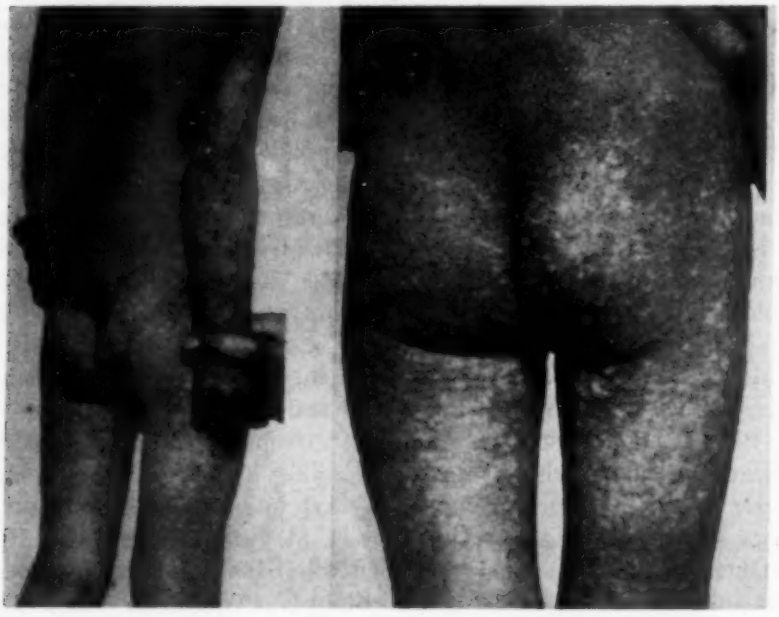


FIG. 28. (Reproduced from paper by R. Seefelder.) Net-like telangiectases surrounding small areas of whitish discolored skin.

The ulcers on both legs, the late appearance of cataracts (not until the third decade of life), presenile appearance and the presence of premature arteriosclerosis are characteristic of Werner's syndrome, whereas the occurrence of telangiectatic scaling areas of the skin, together with pigmentation and depigmentation are considered to be significant of Rothmund's syndrome. It seems, however, to be more justifiable to group the case of Bowmann and Clark under the cases designated as Werner's syndrome, since the characteristics of Werner's syndrome predominated.

R. Seefelder,[34] from the Eye Clinic, University of Innsbruck, reported in an excellent paper "Über familiäres Auftreten von Katarakt und Poikilodermie," a family of six children, two of whom had skin changes with telangiectases and bilateral cataracts; in one only skin changes were noted, and two were healthy. Seefelder recognized the complete similarity of these cases to those reported by Rothmund in

1868. The parents were second cousins. The family lived in one of the completely secluded valleys of South Tyrol, called Val di Non (Nonsberg), which in its seclusion was completely analogous to that valley where Rothmund's children lived. The *skin* changes, which were described as identical, developed in all three affected children at from six to 12 months. They were localized on the face, with the exception of the forehead, on the ears, extensor surfaces of upper and lower extremities, and later they developed on the nates and on the flexor surfaces of the extremities. The arrangement of the lesions was symmetrical. The lesions consisted of small areas of whitish discoloration of the skin surrounded by reddish lines of a net-like appearance. The whitish lesions of pea size represented islets of normal but depigmented skin. The reddish network resulted from an atrophy of the skin. On these areas the skin was slightly depressed and resembled tissue paper, and was somewhat scaling. The red color was due to the fact that atrophic skin becomes translucent and thereby the subcutaneous tissue with its blood vessels was readily visible. Areas of pigmented and depigmented skin were intermixed. Telangiectases were present on face and on the back of the hands. The mucous membranes were not involved. The scalp hair and the *nails* were normal. The diagnosis of the Skin Clinic (University of Innsbruck) was poikiloderma atrophicans vasculare (*Jacobi*[30]). Cataracts rapidly developed at the age of three years in both children and operations were successfully performed. *Endocrine features:* At the age of 12, when the boy was examined, neither testis was descended.

Comment. The similarity of these three children to those described by Rothmund is obvious. The kind as well as the localization of these lesions is identical with the Rothmund type of syndrome under discussion. As in the case described by Schnyder, retardation of the sexual development was marked. R. Seefelder, in agreement with Rothmund, considered the syndrome as a recessive heredofamilial disorder.

A. Marchionini and L. Lux,[35] in 1937, described under the heading "Juvenile Katarakt bei Skleropoikilodermie," the case of an unmarried woman, 30 years old. She exhibited bilateral cataracts, scarce fine grayish scalp hairs and a high hairline (photograph). Menstruation had been regular but painful. The genital organs were atrophic. Pubic hair was very scarce. The fasting blood sugar was high and sugar tolerance curve was characteristic of potential diabetes. Basal metabolic rate was normal. Pigmented and depigmented spots were seen on the skin of the face, on the extensor surfaces of the lower arms and hands. Telangiectases and pea-sized red spots were noted on the face and arms. The skin was in some places indented, shiny and atrophic. A histologic picture of the skin showing hyperkeratosis and an atrophic epidermis was included in the report. The pars papillaris was flat. The author reported a band-like homogenization of the upper layer of the collagenous connective tissue, but this was not evident in the photograph. The subcutaneous tissue was rather loose. The vessels, i.e., the veins, were distended and formed little pools.

Marchionini and Lux classified this lesion as scleropoikiloderma on the basis of the dermatological syndrome described by Jaffe[36] who believed that scleropoikiloderma has features of scleroderma and poikiloderma without being identical with either of these diseases. Marchionini and Lux were not familiar with the original publications of either Rothmund or Werner and, therefore, assumed that their case represented an unknown new syndrome. However, the patient exhibited skin changes identical with the cases described by Rothmund, Siegrist, Schnyder, Bloch and Stauffer and See-

felder. Although cataracts did not develop in this case until the age of 30, it seems justifiable to group the case under Rothmund's syndrome because of the characteristic telangiectatic skin changes occurring simultaneously with atrophy of the epidermis in the afflicted areas and because of the absence of ulcers and arteriosclerosis. As etiological factor Marchionini and Lux suggest "an ectodermal abnormality, which is released by a pluriglandular insufficiency." Such a sequence of events is not, to our knowledge, known in pathology.

Own Case

Patient Sch. was observed 15 years ago and described as "Acromicry with deformities of small phalangeal joints." [37] At that time I was not familiar with Rothmund's syndrome.

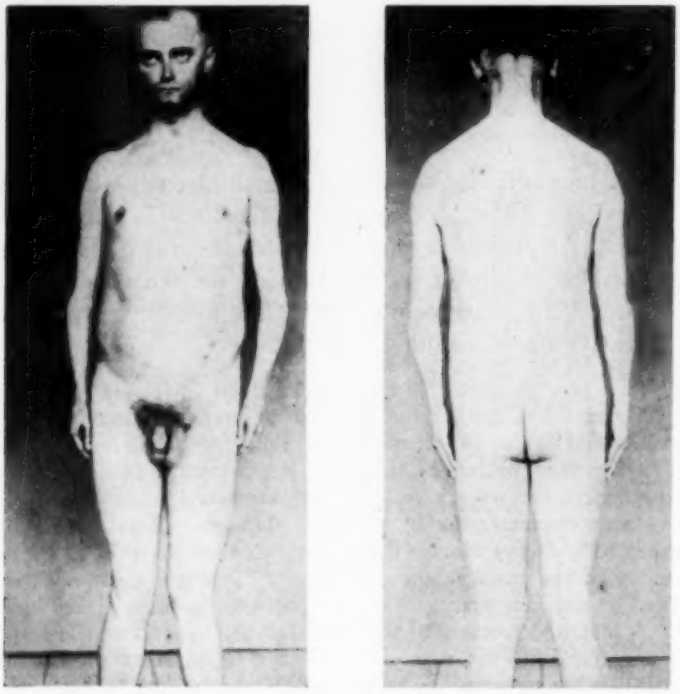


Fig. 29. *Case Sch.* Short stature. Small nose and chin; receding hairline, especially at sides and back of head. Short upper arms and legs. Knock-knees. Scarce pubic hair.

Patient Sch. was 20 years old. No pertinent family history was given. He reported that as a child he had a peculiar reddish, scaling skin on some areas of his body. The skin changes never bothered him. He always felt tired. He came to the hospital because he could not earn a living. His hands were so short and deformed he was unable to work as a laborer. *Appearance:* He was short in stature, 150 cm. His weight was normal. His face did not give the impression of presenility and the appearance of his face corresponded to his actual age. His arms and legs were short. There was an obvious contrast between the lean and short extremities and the normally formed chest and abdomen. He stood and walked with knocked knees.

The feet, and especially, the hands, were very small, the fingers were short, plump and deformed like those of an arthritic person. The motion in the phalangeal joints was slightly limited. The scalp *hairs* were scarce and fine. Over the frontal bone he was almost bald. The hair line in the occipital region was higher than normal. Eyebrows and eyelashes were normally developed. He had a downy beard of fine hairs. He had only a few hairs on chest and abdomen. The axillary hairs were almost absent. The pubic hairs were underdeveloped, coarse and not curled. Symmetrically distributed on both cheeks and on his nose, were small areas of whitish discoloration which were surrounded by reddish lines of the color of telangiectases. The whitish

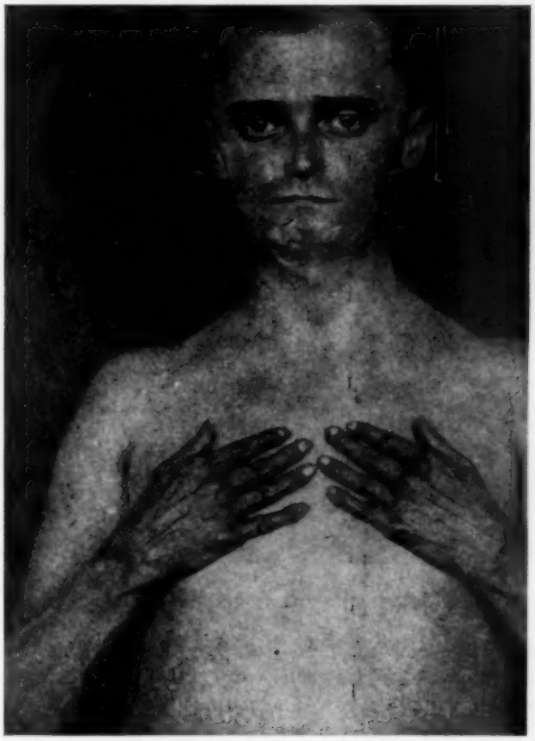


FIG. 30. Net-like telangiectases visible on face, nose, hands, and both sides of abdomen.

areas were scaling and slightly depressed. Also, simple telangiectases in diffuse arrangement were visible. The forehead and the ears were not affected. The skin was rather thin but not taut nor stretched. The mucous membranes were not involved. The same skin changes consisting of areas of whitish discoloration surrounded by a net-like arrangement of telangiectases were noted, especially on the arms, hands and to a minor degree on the lower legs, mainly located on the extensor surfaces of the extremities. Areas of telangiectases were also present on the skin of the lateral parts of the abdomen and symmetrically on both nates. The color of the skin of the affected parts was of a reddish hue, but surrounding the small areas of discoloration, pigmentation in net-like arrangement, apparently in connection with the telangiectases, was observed. The pigmentation was light brown in color and not impressive. The most impressive feature of the skin was the telangiectases and

the pliability of the atrophic skin. A taut, stretched skin was not observed on any part of the body. There were no circumscribed areas of hyperkeratosis and no skin ulcers were present. The subcutaneous fat tissue and the muscles were somewhat underdeveloped on the lower arms and hands. On the lower legs and feet these tissues were also reduced, but not to such a degree as on the upper arms and hands. Nails on hands and feet were normal. On roentgenographic examination the bones of the hands and arms appeared normal for his age. No osteoporosis was seen. The spaces of phalangeal joints of the short fingers were narrowed. There were no changes in the bones themselves. The deformities of the short fingers were probably due to

FIG. 31. Small hands and deformed short fingers. Linear and net-like telangiectases.

changes in the periarticular tissues. His *nose* was small. His *chin* was short. His *voice* was high but not hoarse. His *teeth* were all developed and in good condition. His *ears* were normal in shape. *Eyes:* The patient himself did not complain of visual disturbances, but both lenses showed beginning *opacities* at the lower poles. The lungs and the circulatory organs were normal. Blood pressure was 125 mm. Hg systolic and 80 mm. diastolic. No signs of arteriosclerosis were found. *Endocrine features:* The external genitalia were fairly well developed. Both testes were, however, small in size. The prostate was small. Sexual desire was present.

Comment. The skin changes in our patient had already developed in early childhood as they did in Rothmund's cases. They consisted of small areas of atrophic scaling epidermis surrounded by net-like telangiectases. Since these were characteristic of the skin lesions reported in all cases of Rothmund's syndrome one is justified in diagnosing this case as one of Rothmund's syndrome, in spite of the fact that cataracts did not develop until the age of 20. In Rothmund's original eight cases Karolina Drexel (see page 597) did not develop cataracts. In Nieden's and in Marchionini's case the cataracts developed also at the age of 20 (see pages 601 and 607). Small

hands and feet and short deformed fingers are not observed in all cases of Rothmund's syndrome. This symptom was noted by Seefelder, in the follow-up study of the children originally described by Rothmund, in two instances (see page 607). It was also present in the case of Bloch and Stauffer (see page 602) and in one of the children described by Seefelder (see page 600) as it was observed in our case.

Summarizing the observations which establish *Rothmund's syndrome* as a clinical entity, it is evident that the skin changes are the most characteristic features for differential diagnosis and are present in all cases reported. In contrast to Werner's syndrome the skin is not taut and not tightly stretched over the atrophic underlying structures, but is thin and pliable. Ulcerations are not observed. Marmorization of the skin, due to distended veins and known as livedo-cuticularis in later stages develops to form the characteristic net-like arrangement of the telangiectases around the atrophic scaling area. Owing to formation of telangiectases, the color of the affected skin impresses one as pinkish red, but on closer inspection small white, atrophic areas and brownish pigmented spots are seen in the vicinity of the telangiectases. Since similar features are seen in poikiloderma atrophicans vasculare (Jacobi [30]) the skin lesions in Rothmund's syndrome were also classified as poikiloderma atrophicans vasculare or as scleropoikiloderma. B. Bloch (see page 602) has objected to such a classification, since in poikiloderma atrophicans vasculare telangiectases as well as pigmentation are much more extensively developed and at the same time inflammatory changes in the subcutaneous tissue are found. In the skin lesions of Rothmund's syndrome neither inflammatory reactions (as in poikiloderma atrophicans) nor homogenization of the subcutaneous tissue (characteristic of scleroderma) is found. For this reason the classification as "poikiloderma" or "scleropoikiloderma" is neither in agreement with the histological findings nor with the familial occurrence of this disorder. It seems more appropriate to designate the skin disorder with the purely descriptive term of "heredofamilial atrophic dermatosis with telangiectases" in accordance with the designation of the skin changes in Werner's syndrome as "heredofamilial atrophic dermatosis with skin ulcers."

III. Diseases Related to Werner's Syndrome (Progeria of the Adult), and Rothmund's Syndrome

(*A*) *Cataracta dermatogenes* (*Neurodermitis*) *type Andogsky.* N. Andogsky [38] in 1914 published, under the title "Cataracta dermatogenes," reports on four single and unrelated individuals. These people had suffered from a chronic eczemoid skin lesion from childhood and in the third decade of life developed bilateral cataracts. Similar cases were later published by A. Vogt,[39] A. Löwenstein,[40] A. Siegrist,[27] H. Ollendorf and G. Levy,[41] H. J. Oltmann,[45] Lasló,[43] A. Franceschetti,[46, 47] Metzger.[42] To these 15 cases Ivar

Kugelberg [44] has added two more cases in an extensive survey of this subject.* A. Löwenstein [40] prefers to classify the skin lesions as "neurodermitis," a skin disorder for which, according to I. Kugelberg,[44] the names of ekzema numulare, ekzema en plaques, dermatitis lichenoides pruriens, lichen circumscriptus chronicus (Vidal), pruritus diathésique (Besnier), are found in the literature. Neurodermitis is, according to Kugelberg,[44] a chronic eczematous skin disorder which after childhood develops eczema or complicates ichthyosis. It may also develop independently. The intensity of the inflammation may be marked or slight. Such a process produces lichenification of the skin, neck and the flexor surfaces of the extremities, especially the bend of elbows and knees. The skin in the bends shows a peculiar square formation ("Grobe Felderung," "chagrinization"). In some cases a facies leontina may result from the skin disorder. A histological examination of a skin biopsy is not reported. In some cases asthma and eosinophilia are described. Heredity is reported in only one case of I. Kugelberg.[44] The family tree of this patient showed five generations in which ichthyosis alone, ichthyosis and neurodermitis and asthma occurred interchangeably. Only one member out of the 50 forming the genealogical tree exhibited the combination of ichthyosis, neurodermitis and cataracts.

This case, a boy of 15, had had eczema from the age of six months. At the time of his examination the skin was dry and tight. Fine scales were noticed over the whole body. On the abdomen and shoulders typical ichthyosis was found. Lichenification of the skin was remarkable on the forehead, cheeks and extremities. *Height* was 145 cm. *Teeth:* Two incisors had never developed. *Hair:* Scalp hair was abundant and normal. No pubic hairs were visible. *Eyes:* Bilateral cataract. *Endocrine features:* The thyroid was normal. Basal metabolic rate + 10. Calcium was 13.3 mg. per cent. Roentgen-ray examination revealed normal bones, normal epiphyses and normal sella turcica. Fasting blood sugar was normal. Sugar tolerance was normal. The penis and scrotum were very small and underdeveloped.

Comment. It is possible that this group of patients with juvenile cataracts and features of ichthyosis and neurodermitis may also represent a heredofamilial dermatosis with occasional cataracts. It is, however, evident from the features described as characteristic of Werner's syndrome, as well as of Rothmund's syndrome, that the group of "Cataracta dermatogenes" with neurodermitis differs from these syndromes. Even the heredofamilial occurrence of cataracta dermatogenes with neurodermitis may be doubted since only one case out of 17 had stigmata of heredity.

(*B*) *Progeria of children with nanism* (*Hutchinson-Gilford's syndrome*). Progeria of children (Hutchinson [48]-Gilford's [49, 50, 51] syndrome), also called "nanism senile" or "progero nanie," is a disorder which develops from a few months to three years after birth. In the cases reported the children were normal at birth. There was no history of familial occurrence

* Ten other cases which belong to these groups were described under the title "Atopic Cataracts" by William P. Beetham, Arch. Ophth., 1940, xxiv, 21.

of this disorder or of inter-relationship of the ancestors. The main clinical features observed almost uniformly in all cases were as follows: All the children with progeria looked alike. The published photographs look like the pictures of twins.

All patients were dwarfed in stature. The skull was large in comparison with the face. The frontal and parietal bones were unduly prominent. The fontanels closed early. The scalp hairs were present at birth but became grayish and scarce, and completely disappeared in the course of the disease. There was either very little or no development of the eyebrows. The eyelashes were rare or absent. The faces of these children resemble that of a newly hatched bird. The ears were small, flat, not lobulated, and protruded from the head. The skin of the scalp and face was thin

FIG. 32. (Reproduced from paper by W. A. Manschot.) Patient normal at age of one year.

and of a waxy color. In some areas the skin was taut. The same condition of the skin prevailed on most parts of the body. In some parts, especially over the dorsum of the hands, the atrophic skin was wrinkled like tissue paper. On the thorax and abdomen sharply defined and pigmented areas were seen. There were no ulcers of the skin. The subcutaneous fat on the extremities was poorly developed or almost absent. This was in contrast to the globulous abdomen, where the subcutaneous fat was plentiful. The umbilicus was obliterated. The chest was small. The ribs were prominent and thin. The extremities were short, especially the hands. The feet were flat and small and the fingers were short. Deformities of the phalangeal joints, the knee joints and the ankle joints resembled those of arthritis. The gait of the patient was shuffling as a result of the deformed joints and the tightly drawn skin of the extremities. The muscles on all extremities, like the subcutaneous fat tissue, were poorly developed. The nails were short and crumbly. Proptosis of the eyes simulated true exophthalmos. There was no early cataract observed in the cases published (*V. T. Curtin and H. F. Kotzen,*[52] *E. C. Mitchell and D. W. Goltmann*[53]).

The nose was small and beaked like that of a bird. The chin was retracted. There were isolated, symmetrical fat patches on the lower part of the cheeks and also beneath the mandible, which contributed much to the bizarre aspect of the otherwise taut skin of the face and forehead. The teeth were irregularly placed and carious. The thyroid was not enlarged and not easily palpated. There were normal breath

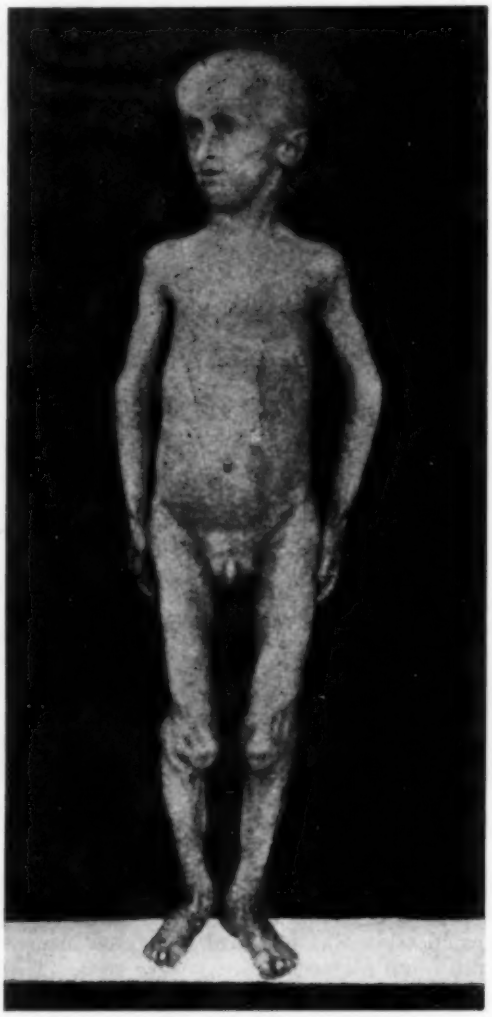


FIG. 33. Patient of Manschot at age of 15. Enlarged hairless scalp, no eyebrows, protruding ears, small mouth. Taut skin, prominent deformed joints of hands and knees. Muscles and fat tissue of both extremities atrophic in contrast to globulous abdomen. Umbilicus obliterated. Sexual underdevelopment.

sounds, and no râles were audible. The heart was normal during the first decade, but in the cases living over 10 years enlargement of the heart was noted simultaneously with a rise in blood pressure. The individual with the longest lifetime of these cases of "progero-nanie" was a 26 year old male reported in the Dutch literature by *W. A. Manschot*.[54] This patient had diffuse arteriosclerosis combined with calcification

of the heart valves. His blood pressure at the age of 11 was 110 mm. Hg systolic and 85 mm. diastolic, at 18,132 mm. Hg systolic and 90 mm. diastolic, at 26, 180 mm. Hg systolic and 120 mm. diastolic. At 26 he suffered from cardiac asthma and angina pectoris and died of cardiac insufficiency as a result of arteriosclerotic heart disease. Liver and spleen were not enlarged as long as the circulation was normal. In later years the liver was found enlarged and the spleen also became palpable (congestion of the liver with slight cirrhosis was found at autopsy). The genital organs were

FIG. 34. Patient of Manschot at age of 26.

normal in the younger cases but in the adolescent cases they were noted as small. Pubic hairs were almost absent. Roentgenograms of the bones showed a characteristic elongation of the necks of the femur (*E. C. Mitchell and D. W. Goltmann* [53]). Osteoporosis was found in some areas; in other places, as in the cortex of the femurs, increased density of the bone was seen. The epiphyseal lines were prematurely closed. Sella turcica was of normal size. Red and white blood cells were normal. Basal metabolic rate was normal. The sugar tolerance curve was flat. Serum calcium and serum phosphorus were normal.

Three autopsies on cases of progeria were reported (*H. Gilford,*[50] *J. Orrico and F. Strada,*[55] *W. A. Manschot* [54]). The main finding was diffuse calcification and sclerosis of the blood vessels. H. Gilford reported an enlarged thymus; Orrico and Strada found a little cyst in the pars intermedia of the pituitary. *W. A. Manschot* [54] believed that the number of eosinophiles in the pituitary was reduced. Other than the

diffuse arteriosclerosis, however, there were no definite lesions of inner organs and endocrine glands evident which could have explained the bizarre appearance of these patients.*

Comment. There is a certain similarity in the features of "Werner's syndrome" and "progeria with nanism" in children. The cases exhibiting Werner's syndrome are short, almost dwarfed in stature. In progeria of children the patients are definite dwarfs. In both syndromes the extremities are short and the abdomen disproportionately large. The fingers and toes are short, and the joints of the extremities are deformed in both instances. The skin is atrophic and taut on the extremities. The panniculus adiposus of the forearm and lower legs is poorly developed as are the muscles, in both disorders. The lack of hair is more pronounced in progeria of children than it is in Werner's syndrome. Sexual retardation is present in both syndromes. Diffuse arteriosclerosis, osteoporosis and the premature senile appearance are the most impressive features present in Werner's syndrome as well as in progeria of children. The autopsy findings in both syndromes are diffuse arteriosclerosis and no definite changes in endocrine organs. Progeria of children, however, differs from Werner's syndrome as follows: (1) There is no familial occurrence. (2) There are no pressure ulcers of the skin. (3) There are no cataracts. (4) The abnormal features develop in early childhood in progeria of children, whereas in Werner's syndrome they become evident in the second decade of life.

It is suggested that progeria of children and Werner's syndrome result from multiple germ plasm defects manifesting themselves at different ages in abiotrophic features of the genotypic kind.

(*C*) *Myotonic dystrophy.* Myotonic dystrophy was first differentiated by I. Hoffman [56] from "congenital myotony" as a separate clinical entity in 1900. It was Steinert,[57] however, in 1909, H. Curschmann,[58] A. Hauptmann,[59] and especially O. Naegeli [60] and his pupil K. Rohrer,[61] who conceived the clinical picture of myotonic dystrophy as a general dystrophy in which the myotonic reaction is not an essential feature of the syndrome. It may even be absent, and only wasting of the entire body and weakness of some muscles may be evident. It was quickly recognized that premature aging, loss of scalp hair, especially on the forehead, atrophic, glossy skin of tissue-like consistency on forearms, hands and lower legs, early cataracts, diminished sexual functions and testicular atrophy are as important in the features of the disease as wasting of some muscle groups or myotonic reaction. In many instances a heredofamilial tendency of the disorder was reported and, especially, the collateral occurrence in brothers and sisters of one generation was observed. K. Rohrer reported an hereditary factor in 23 out of 82 cases. In a complete review of 35 cases in the literature and 15 cases of his own observation, he also emphasized that general weakness,

* While this paper was in press N. B. Talbot, A. M. Butler, E. L. Pratt, E. A. MacLachlan and J. Tannheimer published an article on Progeria of children with metabolic studies and an autopsy report, Am. Jr. Dis. Child., 1945, lxix, 267.

wasting of the subcutaneous fat tissue, skin atrophy, loss of scalp hairs, sexual dysfunction, testicular atrophy, are as characteristic of myotonic dystrophy as atrophy of some muscle groups with occasional myotonic reaction. One of K. Rohrer's cases may be quoted as especially informative in this respect and in view of the relationship of Werner's syndrome to muscular dystrophy.

FIG. 35. (Reproduced from paper of K. Rohrer.) Presenile appearance. Protruding ears. Cataracts.

The *patient* was a 53 year old male. Height was 162 cm. His appearance was atrophic and slender. Subcutaneous fat had almost disappeared. Atrophic skin had been noticed for a long time. At the age of 33 ulcers which did not heal were noted on both lower legs. (His brother also had ulcers on both legs.) There were no varicosities. Some yellowish pigmentation was seen on the flat ears which protruded laterally from the face. Also yellowish patchy pigmentation of the skin of the abdomen was seen. Scalp hairs turned gray very early and were sparse at the time of examination. Pubic hairs were rare. Muscle power of both forearms and hands was diminished after the age of 45. No myotonic reaction was found. Tendon reflexes were normal, but an Achilles tendon reflex could not be elicited because of an ulcer on that tendon. At the time of examination he was only able to do very light work. Both feet were unusually flat. Bilateral cataract was noted at the age of 42. Voice was high-pitched. The heart was normal in size. Blood pressure was 160 mm. Hg systolic. Arteries were slightly tortuous. He married at the age of 26 and had two healthy sons. For several years he did not have any sexual desire.

Comment. It may be granted that in most of the cases of myotonic dystrophy the muscular dystrophy and the myotonic features are the out-

standing features of the disease. General dystrophy and endocrine symptoms may be less evident. Some cases of myotonic dystrophy, however, as the patient reported by Rohrer, demonstrate the close relationship of myotonic dystrophy to Werner's syndrome. It may be mentioned that an outstanding neurologist who examined one of our cases (Sidney O.) ventured the diagnosis of myotonic dystrophy in this case of obvious Werner's syndrome, although myotonic features were absent.

(*D*) *Hereditary ectodermal dysplasia, dystrophy of hair and nails (Type McKay and Davidson).* As hereditary ectodermal dysplasia of the "anhydrotic type" [63] (Type Widderburn) an anomaly is described, which is characterized by complete inability to sweat (anhydrosis), a deficiency of the scalp, axillary and pubic hair (hypotrichosis), and incomplete development of the teeth (anodontia). This type is restricted as to sex and only males are affected. From this anhydrotic type of ectodermal dysplasia McKay and Davidson [62] differentiate a group in which the sweat and sebaceous glands are present and perspiration occurs but hair and nails are dystrophic. In these cases keratoderma plantaris et palmaris is observed. The skin is otherwise normal in appearance. This type, in contrast to the anhydrotic type, is transmitted by both sexes and manifests itself through many generations.[63] The hyperkeratosis plantaris, the loss of scalp hairs, bear some similarity to Werner's syndrome. The differentiation is obvious, however, since neither general dystrophy of the body, cataracts nor presenility is observed in "hereditary ectodermal dysplasia." In this syndrome the clinical features result only from a defect of the ectodermal germinal layer, whereas in "Werner's syndrome" and even more obviously in "progeria of children" multiple defects of the germ plasm produce various abiotrophic changes of organs deriving not only from the ectoderm but also from the other germinal layers.

General Comment

As seen from various publications quoted from the world's literature, there is considerable confusion in recognizing Werner's and Rothmund's syndromes as different although related clinical entities. This is the more astonishing for the striking resemblance of cases of one family affected with one of the syndromes to cases of another family. The striking differences of Werner's syndrome and Rothmund's syndrome are as follows:

(1) Werner's syndrome starts at the *age* of 20 to 30, beginning with graying of the hair. Later skin changes and cataracts develop. Rothmund's syndrome begins in early childhood. The skin changes are already visible three to six months after birth. Cataracts develop also in childhood, namely, from three to five years of age.

(2) The *shortness of stature* is more outstanding in Werner's syndrome than it is in Rothmund's syndrome.

(3) The *skin changes* are different in their features in both syndromes. In Werner's syndrome the most striking feature is tightening of the skin

Symptoms	Werner's Syndrome	Rothmund's Syndrome	Cataracta Dermatogenes with Neurodermitis	Progeria of Children with Nanism	Myotonic Dystrophy	Ectodermal Dysplasia with Dystrophy of Hair and Nails
Heredofamilial occurrence	+++	+++	±	0	++	+++
Age at the beginning of disorder	20–30 y	3 mo.–3 y	3–20 y	2–5 mo.	20–30 y	shortly after birth
Shortness of stature	+++	+	0	++++	+	0
Skin changes	++++	++++	++++	+	+	++
a) Tightly drawn over underlying tissue	++++ 20–30 y	0	0 3–20 y	+ 2–5 mo.	+ 20–30 y	0 shortly after birth
b) Atrophic and thin skin	++++	++	++	++	++	+
c) Telangiectases	+	++++ 3 mo.	0	0	0	0
d) Scaling	++	++++	++++	+	0	0
e) Pigmentation and depigmentation	+	+++	++	+	+	0
f) Ulcers	++++	0	0	0	+	0
Canities of scalp hairs Age	++++ 20–30 y	± 40 y	0	++++ 2–5 mo.	+++ 20–30 y	Bald
Sparse sex hairs	+++	++	0	+++	+++	0
Muscular atrophy on distal parts of extremities	+++	±	0	+++	+++	0
Atrophy of the subcutaneous fat tissue	+++	±	0	+++	+++	0
Bilateral cataracts	++++ 20–30 y	++++ 3–4 y	±	0	+++ 20–30 y	0
Diffuse arteriosclerosis	+++	±	0	++++	++	0
Osteoporosis	+++	0	0	++	+	0
Joint deformities	+++	+	0	+++	+	0
Thyroid	+	0	0	0	+	0
Proptosis	+++	0	0	++++	0	0
Sexual underdevelopment	++++	++	0	+++	+++	0
Myotonic reaction	0	0	0	0	++	0

over the underlying structures which are very poor in subcutaneous fat tissue. The skin changes are localized on the lower legs and feet and, to a lesser degree, on the forearms, hands and face. The ears are only slightly deformed and there is little involvement of the skin over the ears. Circumscribed hyperkeratotic areas of shell-like appearance are present on the soles beneath the great toes and heels. Ulcers develop mainly on the points of pressure on heels and toes, over the ankles and, especially, over the Achilles tendon. The fact that skin can be successfully grafted on the ulcerated areas demonstrates that the ulcers are not entirely trophic in origin but due to pressure on areas where the skin is tightly drawn over the bone without any padding of subcutaneous fat tissue. The classification of these skin disorders in the literature as "scleroderma" or "scleropoikiloderma" does not correspond to the clinical or histological findings. The characteristics of true

scleroderma, namely, sclerosis of the skin and homogenization of the subcutaneous tissue, are not present, but there is atrophy of the skin, flattening of the rete and of the papillae. The most impressive feature, however, is the poorly developed panniculus adiposus beneath the involved areas in the distal parts of the arms and legs. It seems that the disappearance of the subcutaneous fat tissue which apparently occurs simultaneously with the atrophy of the superficial layers of the skin results in tightening of the skin over the underlying structure and simulates scleroderma. Inflammatory changes of the blood vessels (arteries) which are found in true scleroderma are not present. Calcium deposits in the walls of the subcutaneous blood vessels, however, are seen in the most progressed cases. Since the skin changes in Werner's syndrome only simulate true scleroderma but are in no way identical with this disease, the classification as scleroderma should be rejected. A descriptive name as "heredofamilial atrophic dermatosis with skin ulcers" seems to be more appropriate.

In Rothmund's syndrome the skin lesions are in evidence five months after birth. In contrast to Werner's syndrome there is neither stretching of the skin nor the presence of ulcers. The first changes occur on the skin of the face, ears, on the cheeks, on the buttocks, and later the skin over the knees and extensor surfaces of the extremities is involved. The flexor surfaces show lesions late, or not at all. The vola manus and the bend of elbows and knees remain free. In the first stages the skin changes correspond to the livedo reticularis and exhibit, therefore, a reddish hue. Reddish striae, round reddish spots with telangiectases appear later on. The color of the lesion changes to a yellowish scar tissue which scales slightly. Normal skin encircled by such yellowish scar tissue acquires a characteristic areolated appearance. The areas of the skin not involved are extremely fine, soft, and translucent, causing the smallest ramifications of the skin veins to become visible. The skin on the hands and feet is pliable and thin as tissue paper. Some scattered telangiectases are also seen in these areas. Pigmented and depigmented areas are more pronounced than in Werner's syndrome. The classification of these skin changes as scleropoikiloderma does not coincide with the features described. A descriptive designation of the skin lesions in Rothmund's syndrome as "heredofamilial atrophic dermatosis with telangiectasis" seems more appropriate.

(4) Histological examination of the skin shows, in both cases, atrophy of the mucous layer, flattening of the papillae, even complete disappearance of the rete pegs. The changes typical of scleroderma and scleropoikiloderma were absent; there were neither inflammatory changes of the subcutaneous tissue and of the blood vessels nor sclerosis or homogenization of the collagenous tissue. The difference between the histological changes in Werner's and Rothmund's syndromes is the distention of the veins. In Werner's syndrome only occasional distention of the veins is found in the subcutaneous tissue whereas in the affected parts of the skin in Rothmund's syndrome the veins are generally distended and may even form small pools.

(5) The *muscles* and *the subcutaneous fat tissue* of the distal parts of the extremities in Rothmund's syndrome are less atrophic than in Werner's syndrome. In childhood the muscles of Rothmund's syndrome are, in this respect, normally developed. In the few cases of Rothmund's syndrome observed at a later age muscular atrophy occurs on forearms and lower legs. Fingers and hands remain small and short in both syndromes.

(6) *Cataracts* are of the same kind in both syndromes. They develop as star-like opacities in the periphery of the lens, mostly on the posterior pole. However, the age at which the cataracts begin to develop is significant. In Rothmund's syndrome they are already formed in early childhood, that is, at the age of three to five; in Werner's syndrome they develop in adult life, between the age of 20 and 30.

(7) *Canities* is the earliest feature of Werner's syndrome. It appears in the early twenties. The children exhibiting Rothmund's syndrome have abundant scalp hairs of normal color; even in the cases observed at a later age canities is not an outstanding feature.

(8) Diffuse *arteriosclerosis* is evident in Werner's syndrome in all cases and results in early complications involving the circulatory system, such as gangrene or heart failure. In Rothmund's syndrome diffuse arteriosclerosis is not observed in young patients. Patients exhibiting Rothmund's syndrome in childhood may reach an old age, as Seefelder's follow-up study of Rothmund's cases shows. In some cases, however, as in Bloch and Stauffer's case, arteriosclerosis developed in the fourth decade of life.

(9) *Osteoporosis* occurred in all cases of Werner's syndrome in which roentgen-ray studies of the bones were made. In Rothmund's syndrome osteoporosis was not observed.

(10) Dysfunction of the *thyroid* was noticed in some patients exhibiting Werner's syndrome. In some patients a goiter was found; in some patients the thyroid could not be palpated at all. Symptoms of hyperthyroidism were not present in any of these patients. Proptosis of the eyes found in most of these patients is not due to hyperthyroidism. In Rothmund's syndrome dysfunction of the thyroid was not observed. These patients do not show proptosis.

(11) Underdevelopment of the *sex organs* and of the pubic hair is found in all cases of Werner's syndrome. In males, however, erections and the ability to have intercourse seem to have been preserved for some time. Most of the females described did not marry but had menstruated at least for some time. The patients exhibiting Rothmund's syndrome showed, in most cases, normal sexual development during puberty. In some male cases, however, retardation of sexual development and, later, atrophy of the testes was noted. Those females of the families described by Rothmund who exhibited both skin changes and cataracts were childless, whereas those females who had only skin changes produced children.

(12) The bizarre changes of the epithelium of the vocal *cords* causing a *hoarse, high pitched voice,* were found only in patients exhibiting Werner's

syndrome. High pitched voices may occur in Rothmund's syndrome due to sexual retardment but the characteristic changes of the surface of the vocal cords were never observed in cases with Rothmund's syndrome.

(13) Tendency to *diabetes* or diabetic glycosuria is observed in cases of Werner's syndrome but not in Rothmund's syndrome. The tendency to diabetes seems to parallel the progress of arteriosclerosis. The occasional observation of gangrene of the lower legs is the result of a secondary infection of the pressure ulcers but aggravated by the presence of arteriosclerosis.

The comparison of features of both syndromes under discussion shows that Werner's, and Rothmund's, syndromes are heredofamilial disorders with atrophic dermatosis, bilateral cataracts and endocrine features. Striking differences, however, are evident in the skin changes, as well as in the time and in the site of their occurrence. The difference in the appearance of the patient, especially in respect to the symptoms of presenility (progeria) justify separating Werner's and Rothmund's syndromes into two different but related clinical entities.

(14) Both syndromes may not develop in all their features and may occur as "forme fruste." Intimate acquaintance with the syndromes under discussion may facilitate their recognition even as forme fruste. Thus, more families stricken with these heredofamilial disorders will be discovered, bearing out my contention that the disorders are not so rare as now believed.

Etiology

The survey of all cases demonstrates clearly that Werner's, as well as Rothmund's syndrome, is a recessive hereditary disorder. This conception cannot be altered by the occasional occurrence of cases with a normal family history. It is a special feature of these particular heredofamilial disorders that they occur collaterally in one generation. Werner, as well as Rothmund, suggested that we are dealing with a disorder of the ectodermal layer, since both skin and lens are derived from the ectoderm. Such a theory is not substantiated by the multiplicity of symptoms, involving blood vessels, subcutaneous fat tissue, muscles and endocrine glands; especially not since we know the symptom complex of a heredofamilial disorder involving only the ectodermal layer—"ectodermal dysplasia of the anhydrotic and hydrotic type," which is entirely different from the syndromes under discussion.

Such authors as Bloch and Stauffer favor a primary endocrine disorder which is reflected in the skin as an explanation of the pathogenesis of the syndromes. Oppenheimer and Kugel, who reported an autopsy of a case of Werner's syndrome, found the parathyroid hyperactive. The Hamilton-Schwartz test was positive during life. These authors were inclined to attribute an etiological significance to the hyperactivity of the parathyroids. Oppenheimer, however, in a personal communication, states that he no longer adheres to the opinion that the parathyroid gland is predominately involved.

It is not unusual that in chronic diseases of young individuals the functions of the endocrine glands are impaired. The physical development of the body, growth as well as sexual maturity, suffers if other organs, like heart, lungs or kidneys, are congenitally underdeveloped. This may be so in our syndromes. The endocrine dysfunction may then be secondary to the heredofamilial constitutional skin disorder.

The heredofamilial character of the syndromes under discussion, however, is indicative of a more basic nature of its pathogenesis. This points to a defective germ plasm which manifests its multiple defects at different periods of life. The multiple defects result in abiotrophic processes not only of organs which originate from the ectodermal layer, but also of organs which originate from the other germinal layers. The only certain fact bearing on the etiology of these syndromes is its heredofamilial nature. For this reason the occurrence of defects of the entire germinal plasm, recessive in heredity, seems the most plausible explanation of the pathogenesis of Werner's as well as Rothmund's syndrome.

Summary

1. The symptomatology of Werner's syndrome is established and demonstrated in cases from the literature and in four of our own. With the exception of Oppenheimer and Kugel's cases, the cases of Werner's syndrome in the literature are published under the misleading designation "Scleroderma and Cataracts."

2. The skin changes in Werner's syndrome are not those of true scleroderma. Because of its recessive heredofamilial occurrence it is suggested that the skin changes, as the other symptoms of Werner's syndrome, are the result of a defective germ plasm not manifesting itself until the second and third decades of life. A general term for the designation of the disorder as "progeria of the adult" is suggested since all symptoms of Werner's syndrome result in presenility of the patient.

3. The designation of the skin changes with a purely descriptive name, as "heredofamilial atrophic dermatosis with skin ulcers" seems more appropriate.

4. The skin ulcers in Werner's syndrome are not entirely trophic in origin since they appear only on exposed parts and are probably the result of pressure upon the thin, atrophic and stretched skin. The healing of the ulcers by grafting skin upon the skin defects supports such an opinion.

5. The symptomatology of Rothmund's syndrome is illustrated by cases selected from the literature and by a case of our own.

6. The skin changes of Rothmund's syndrome are classified in the literature as "poikiloderma" or "scleropoikiloderma." Such a classification does not accord with the heredofamilial occurrence of the skin disorder nor with the histological findings. In conformity with the designation of the skin disorder in Werner's syndrome it seems appropriate to use for the skin

changes in Rothmund's syndrome a simple descriptive name such as "heredofamilial atrophic dermatosis with telangiectases."

7. Both syndromes may occur as incomplete forms, so called "forme fruste."

8. The heredity in both forms is recessive. The collateral occurrence in brothers and sisters of one generation is often observed. Rothmund's syndrome starts usually in childhood; Werner's syndrome in the second and third decades.

9. Clinical syndromes related to Werner's and Rothmund's syndromes are discussed. A chart tabulating the features of Werner's and Rothmund's syndromes in comparison with related clinical entities is presented to aid in the differential diagnosis of these syndromes.

10. For the pathogenesis of Werner's syndrome and Rothmund's syndrome a purely ectodermal dysplasia as well as primary endocrine functional disturbance is rejected. The recessive heredity of both syndromes suggests as an explanation for its etiology the existence of multiple germ plasm defects manifesting themselves in abiotrophic features of various organs at different periods of life.

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ABSORPTION AND EXCRETION OF IRON*

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Considering the importance of iron in the body and the extensive work that has been done on this subject, still relatively little is known concerning metabolism of iron. During most of the last century many extensive arguments were carried on as to whether or not iron was absorbed at all. The misconception that it was not absorbed arose from the fact that the small amounts of iron in the body could not be detected by chemical methods available at the time. As late as 1893, Stockman [1] felt it necessary to refute the theory, which was apparently current then, that the action of iron in chlorosis arose from the precipitation of poisonous hydrogen sulfide in the intestine. This he did satisfactorily by successfully treating patients who had chlorosis with subcutaneous injections of citrate of iron. During the first part of this century, mainly under the influence of the histologic school, a theory of metabolism of iron was evolved which has more or less continued to be in vogue. The most widely accepted current theory has been succinctly stated in Starling's "Human Physiology" [2]: "The absorption of iron takes place in the duodenum and upper part of the jejunum. Only 1 or 2 mg. appear in the urine, all the rest being excreted in the large gut and appearing in the feces, chiefly as sulfide of iron." In other words, this view assumes that iron is absorbed from the upper part of the intestine regardless of stores in the body. The excess is then secreted by a specific action of the colonic mucosa.

Before the present work was undertaken, reports of the previous investigations were thoroughly surveyed and references to them are given in the thesis which forms the basis of this paper. The main purpose here, however, is to report any contribution we ourselves may be able to make on the subject.

Rationale and General Method of Present Work

The work reviewed seemed to show fairly definitely that iron is not excreted by the dog. However, investigations based on human subjects are open to criticism from three points. First, in experiments that necessitate administration of iron by mouth, the difficulty is encountered of determining

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From the Mayo Foundation (Fellow in Surgery, Dr. Little) (Division of Biochemistry, Dr. Power) and Mayo Clinic (Division of Medicine, Dr. Wakefield). Since this paper was written Dr. Little has entered the army and is now an officer of the Medical Corps, Army of the United States.

many grams of iron in a large volume of stool with accuracy within a few milligrams. Second, after administration of iron by mouth two to four weeks are required for the intestine completely to eliminate the dose, as most of it is precipitated as iron sulfide, which tends to adhere to the mucosa and is passed slowly. Third, with the administration of iron by mouth, the additional variable factor of absorption, which is impossible of determination and control, must be considered.

In the present work we have tried to circumvent these difficulties by intravenous administration of the iron. In this way it is possible to be sure of the amount of iron that reaches the interior of the body and large quantities do not have to be determined in the stools over long periods of time. In general, the iron in the feces was determined during three successive periods. The first and third periods were used as controls and, during the second period, iron was injected intravenously. This sequence does not apply to the study reported as third in this paper and summarized in table 3, which will be referred to again later.

Details of Procedure

The metabolic processes of the three subjects used apparently were satisfactory. They had been in an institution for several months on an adequate diet and could be assumed to have ingested adequate quantities of iron. Their stools were repeatedly negative for blood by the benzidine test. During the entire time of the study they were kept in a hospital ward where they could be observed. During the test periods they were placed on diets of approximately constant daily content of iron, as calculated from accepted analyses. Urine and stools were collected separately by means of a special, nonferrous bifurcated commonde, stools were separated into periods by means of carmine markers. The receptacles were two glass containers which previously had been rinsed with diluted hydrochloric acid. Collections of blood were made from veins of the arm, with a stainless steel 18 gauge needle. To prevent hemolysis, a tourniquet or a syringe was not used. The first 10 c.c. of blood were allowed to flow into a tube that contained heparin and were used to ascertain the value for hemoglobin, the number of erythrocytes per cubic millimeter and hematocrit values. The next 10 c.c. were collected under oil for determinations of serum iron.

The iron was administered as ferrous ascorbate. This compound was first described by Szent-Györgyi [3] and has been used fairly extensively by Heilmeyer,[4] by Fleischhacker and Schürer-Waldheim [5] and by Friend.[6] This compound was chosen because it can be safely administered in sufficient quantities. Our supply of ferrous ascorbate was prepared by us after the method of Maurer and Schiedt.[7] Each preparation was analyzed for content of iron and was kept in a desiccator. At the time of use a quantity was weighed which would contain the desired amount of iron. This was dissolved in 200 to 300 c.c. of physiologic saline solution and was immediately

injected. The injections contained 30 to 40 mg. of iron each and were given in a period of 45 to 75 minutes. Faster administration caused mild symptoms, characterized by warmth and flushing of the face. There were no late symptoms and only one episode of thrombosis. The thrombosis followed several injections into the same vein.

Analytic Procedure

Determination of iron in blood serum was accomplished by a modification of the procedure described by Moore.[8] The modified procedure was as follows:

Ashing. Five (or 10) c.c. of serum were measured into a 100 c.c. Kjeldahl flask, followed by 5 (or 10) c.c. of concentrated nitric acid and two glass beads. The mixture was heated by means of a microburner over wire gauze, gently at first, then somewhat more vigorously so that the volume was reduced to 2 to 3 c.c. during about 30 minutes. The flask was allowed to cool for one to two minutes; then 2 c.c. of 70 per cent perchloric acid were added, and the heating over wire gauze was continued with the flame adjusted so that the nitric acid remaining in the digest was distilled off in about 15 to 20 minutes. With the appearance of the white fumes of perchloric acid, which indicated that the major part of organic matter had been destroyed, the heat was increased and the solution was heated vigorously over the free flame for 30 to 40 minutes longer to remove all traces of yellow or green color. The digest was then allowed to cool, the sides of the flask were rinsed down with 3 to 4 c.c. of iron-free distilled water, and the mixture was boiled until the added water was distilled off; then the mixture was heated more vigorously for another 15 to 20 minutes. The digest was again cooled, 10 c.c. of distilled water were added, and the mixture was boiled for one to two minutes. The flask was then removed from the flame, a drop of concentrated nitric acid was added to the hot solution, followed by 10 c.c. more of distilled water. Known amounts of iron to serve as standards for colorimetric comparison, 5 or 10 gamma in each sample, were carried through the above procedure, with the same amounts of the various reagents.

Development of Color. To each unknown and standard, prepared as has been described, were added 6 c.c. of iso-amyl alcohol and 3 c.c. of 20 per cent solution of sodium thiocyanate. (The flasks containing the solutions were cooled somewhat below room temperature before the addition of the alcohol.) After the red iron sulfocyanate complex had been extracted into the alcohol layer, by shaking the flasks for two to three minutes, the colored layers were pipetted off directly into 20 mm. absorption cells for determination of light absorption by means of the Pülfrich photometer, or into the small test tubes used with the Klett-Summerson photo-electric colorimeter. With the latter instrument, the green filter number 54, with maximal light transmission at wave length 540 mm., was used.

Determination of Iron in Feces. The total amount of feces collected in each period was treated with four 50 c.c. portions of concentrated nitric acid for several days, until the mixture was homogeneous, after which aliquots of 25 to 30 gm. were weighed into Kjeldahl flasks of a capacity of 300 c.c. These samples were then ashed with nitric and perchloric acids, and the iron thiocyanate color complex was developed, extracted and determined essentially as described for serum.

Results

Table 1 shows the results obtained with the first subject. This was a man, 46 years of age, afflicted with syphilis of the central nervous system but otherwise in good health. The total time of study consisted of 26 consecutive days which were divided into three periods of nine, ten and seven days respectively. During the second period a total of 311 mg. of iron was administered intravenously in eight injections.

Table I

A Man, 46 Years of Age, Who Had Syphilis of the Central Nervous System. Iron Administered Intravenously during Second Period. Patient on Constant Diet during Test

		Period 1 9 days	Period 2 10 days	Period 3 7 days
Iron, gamma per 100 c.c. serum	Begin	216	186	145
	End	186	145	232
Hemoglobin, gm. per 100 c.c. blood	Begin	13.5	13.5	13.5
	End	13.5	13.5	13.5
Erythrocytes, millions per cu. mm. blood	Begin	3.99		4.34
	End		4.34	4.35
Volume packed erythrocytes (hematocrit)	Begin	43.4		43.9
	End		43.9	46.8
Iron given in period, mg.		0	311	0
Iron in urine, mg.	Total for period	0.41	7.01	
	Daily average	0.04	0.70	
Iron in stools, mg.	Total for period	159.0	152.2	109.3
	Daily average	17.7	15.2	15.6

The concentration of hemoglobin, the erythrocyte count and the volume of packed erythrocytes remained approximately constant during the study. The small variations in the last two might possibly be due to the fact that the determinations were made on heparinized blood several hours after collection. The value for serum iron was somewhat high, varying from 145

to 232 gamma per 100 c.c. During the period of study the value did not change significantly, however. The iron in the urine during the first control period totaled 0.41 mg., or an average of 0.04 mg. daily. This increased during the period of administration of iron to a total of 7.01 mg., or a daily average of 0.70 mg. The daily fecal iron remained essentially constant during the three periods, being 17.7 mg., 15.2 mg. and 15.6 mg., respectively.

TABLE II

A Man, 36 Years of Age, Who Had Syphilis of the Central Nervous System. Iron Administered Intravenously during Second Period. Patient on Constant Diet during Test

		Period 1 4 days	Period 2 8 days	Period 3 5 days
Iron, gamma per 100 c.c. serum	Begin	115	86	
	End	86	46	
Hemoglobin, gm. per 100 c.c. blood	Begin	11.4	11.6	
	End	11.6	10.8	
Volume packed erythrocytes (hematocrit)	Begin	40.5	41.8	
	End	41.8	35.6	
Iron given in period, mg.		0	156	0
Iron in stools, mg.	Total for period	26.6	48.9	32.6
	Daily average	6.6	6.1	6.5

Table 2 shows the results noted in a study of a paretic man 36 years of age. He was followed during 17 consecutive days, divided into three periods of four, eight and five days each. During the second period he was given 156 mg. of iron in four injections.

The concentration of hemoglobin and volume of packed erythrocytes remained essentially constant. The values for serum iron were somewhat

TABLE III

A Man, 40 Years of Age, Who Had Schizophrenia. 30 mg. of Iron Administered Intravenously. Injection Started at 7:15 a.m. and Concluded at 7:45 a.m.

	Volume Urine, c.c.	Total Iron Excreted, mg.	Average Excretion per Hour, mg.
Period 1—1 hour, 30 minutes (7:15 a.m. to 8:45 a.m.)	175	0.19	0.13
Period 2—4 hours, 45 minutes (8:45 a.m. to 1:30 p.m.)	200	0.06	0.01
Period 3—3 hours, 30 minutes (1:30 p.m. to 5 p.m.)	200	0.03	0.01

Total excretion in approximately 10 hours, 0.29 mg.

low, varying from 46 to 115 gamma per 100 c.c. The accuracy of the 46 gamma is probably questionable. The average daily fecal iron remained fairly constant, being 6.6 mg., 6.1 mg. and 6.5 mg. for the respective periods.

Table 3 shows the results obtained from further study of urinary excretion following intravenous injection. The subject was a man, 40 years of age, who was suffering from schizophrenia. Iron, 30 mg., was given intravenously and the urine was collected at intervals during the following approximately 10 hours. The total excretion during this period was only 0.29 mg., 0.19 mg. of which appeared during the first 90 minutes.

Summary and Comment

Determination was made of the amount of iron in the feces of two men whose iron reserve apparently was normal. Injection of relatively large amounts of iron by vein caused no detectable increase in the fecal iron. This conclusion is in agreement with the results obtained in dogs by Henriques and Roland,[9] Hahn and associates [10, 11, 12] and Quinke.[13] It would tend to lend confirmation to the hypothesis advanced by McCance and Widdowson [14, 15] that the body has no mechanism whereby an excess of iron can be excreted. Over a control period of nine days one of these two men was found to excrete approximately 0.045 mg. of iron per day in his urine. This is somewhat lower than the determinations of Farrar and Goldhamer [16] who found 0.02 mg. per 100 c.c. and those of Henriques and Roland who estimated 0.08 to 0.32 mg. per day.

As found in study of a third man, following intravenous injection of iron there is a marked increase in the amount of urinary iron. This has been found by other observers. The total amount was relatively small, however, being only 0.29 mg. within 10 hours following the injection of 30 mg. More than 65 per cent of this appeared within the first 90 minutes. This increased excretion is apparently due to the sudden and marked increase of iron in the blood and probably does not take place following its normal absorption from the intestine.

We are aware that, at postmortem examination in cases of general paralysis of the insane, pigment is found in the brain. This pigment is known to be iron and is associated with the local degenerative changes. We do not believe that this deposition substantially disturbs the systemic metabolism of iron. Nevertheless, the phenomenon should be mentioned here for its possible significance as knowledge is extended.

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VENTRICULAR TACHYCARDIA—A REPORT OF TEN CASES, EIGHT OF WHICH WERE TREATED WITH QUINIDINE WITH RECOVERY IN SEVEN *

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REVIEW of the recent literature reveals little dealing with the effects of large doses of quinidine on ventricular tachycardia. No series comparable in size to this one has been noted within the past 15 years. McMillan [1] recently reported two cases following coronary thrombosis treated successfully with quinidine. Reich [2] reported a cure with a total of 185 grains given in a period of two and a half days, a dosage believed by him and also by Levine [3] and Gold [4] to be the largest dose given in a period of 60 hours. Some of the cases in this series had quinidine in doses approaching the amount given by Reich, with a favorable outcome. In Reich's case a QRS interval greater than 0.18 second was avoided for fear of producing ventricular fibrillation. It is not believed that the QRS duration as influenced by quinidine should be used as an index of quinidine poisoning in the therapy of this arrhythmia. In some of the cases of this series the gradual spread of the QRS interval well exceeded the arbitrary limit of 0.18 second with no observable detrimental effect—indeed the lengthening of the interval was a probable factor in the termination of the arrhythmia. It was invariably associated with a slowing of the ventricular rate and often with a feeling of well being.

Levine and Fulton [5] gave as much as 112 grains of quinidine in 24 hours to a patient with ventricular tachycardia. Viko, Marvin and White [6] gave daily doses up to 60 grains. In recent years the trend has been to exceed by far the recommended dose of 15 to 30 grains daily. Levine has recently recommended large doses e.g., 15 grains every four hours in the treatment of ventricular tachycardia complicating coronary thrombosis. Fishberg [7] states that he has failed to abolish the rhythm in two cases following coronary thrombosis "perhaps because the maximum dose recommended by him (Levine) was not given."

Williams and Ellis [8] did not evaluate the results of quinidine therapy in the 36 cases from the files of the Boston City Hospital because of the lack of uniformity in the treatment of this arrhythmia and also because the dosage administered was much too low. They stated that in "certain individual cases the value of the drug seems unquestioned. Even if the drug

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does not abolish the attack, a slowing of the rate often occurs and produces improvement in the circulation."

Woodruff [9] feels that quinidine is absolutely indicated in ventricular tachycardia. He also is of the opinion that treatment should be started early and that the dose of quinidine should be large. He mentions the prophylactic administration in cases of coronary thrombosis, so often stressed by Levine. He discusses the method of administration proposed by White using six grain doses every two hours for five doses during the day and repeating as often as is necessary until a normal sinus mechanism is restored. He states that larger doses may sometimes be required.

Stempien and Katz [10] reported a case of this arrhythmia successfully treated with quinidine augmented with potassium. These authors are of the opinion that quinidine "is by far the most reliable drug in the treatment of paroxysmal ventricular tachycardia." They are quite impressed with the favorable result in the therapy of this case, and attribute a large measure of the success to the simultaneous use of the potassium. It may be stated at this point that atropine has also been suggested as an adjunct by Levine. We have had insufficient experience to attempt any evaluation of these secondary drugs in the treatment of this ectopic rhythm.

With respect to Levine's suggestion as to the use of quinidine following coronary thrombosis in the anticipation of the arrhythmias, Master feels that the administration of this drug is dangerous in the acute stages. Furthermore he feels that its evaluation in the acute stages is fraught with uncertainty in view of the relatively transitory nature of the arrhythmias in this condition. Comeau [11] feels that quinidine is the drug of choice in the treatment of ventricular tachycardia.

Kerr is not enthusiastic about the use of quinidine in the control of ventricular tachycardia. He feels that the paroxysms are transient in nature and that conclusions are drawn only with great difficulty. However, it seems to the writer that the close relationship between the administration of the drug and the favorable outcome in a great number of the reported cases, and in the cases of this series, is too obvious to indicate anything other than a causal effect in the termination of the arrhythmia. It must also be stated that no untoward effect was noted in this series, the rhythm having been successfully terminated in seven of the eight treated cases.

A word must be included at this time with respect to the usage of quinidine. In accordance with the Government's policy regulating the use of this critical drug, its administration has been restricted to attacks of ventricular tachycardia, to coronary thromboses complicated by frequent extrasystoles, and to prolonged attacks of paroxysmal supraventricular tachycardia uncontrolled by the usual methods, including the use of mecholyl. The administration of the drug is closely supervised by the cardiac service. Perhaps, on occasion, we have exceeded the maximum allowable dose but it was only because we honestly felt that it would have a life saving effect.

The 10 cases reported here have been observed within a period of four years, the high incidence no doubt resulting from the type of patient seen in this 600 bed general hospital. The patient load is practically entirely male and the average age of veterans of World War I today is slightly over 51 years. It is thus seen that an opportunity is provided for the study of a selected group of patients of an appropriate sex and age with respect to the degenerative vascular lesions. Ample facilities exist for detailed cardiovascular studies.

Case Reports

Case 1. A 50 year old white lawyer had known cardiac disease with anginal syndrome since December 1943. There was no history of a previous coronary thrombosis and he had never shown signs of a failing myocardium other than the angina of effort which was of mild to moderate severity. He was not a known hypertensive. At 8:45 p.m. on October 14, 1944, he was admitted in an apparently terminal state with the history of the onset of severe oppressive retrosternal pain at about 5 p.m. on that day. At the time of admission he was cyanotic and in shock. The pulse was imperceptible and no blood pressure reading was obtainable. The ventricular rate was 140 and apparently regular. (He was not seen by the author.) There was an apical gallop present; no friction rub was heard. Electrocardiogram showed a ventricular tachycardia. He died at 8:05 a.m., October 15, 1944.

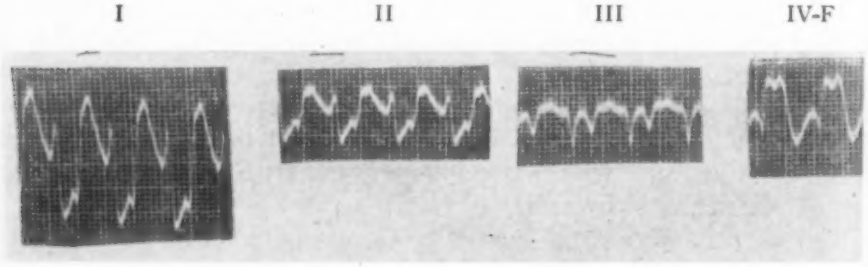

Fig. 1. *Case 1.* This was the presenting tracing on a patient who died promptly after admission. He received no quinidine. Clinically he presented findings suggesting a massive infarction. Postmortem examination revealed a large hemorrhagic infarction of the anterolateral wall of the left ventricle.

Summary. A 50 year old white male, with known anginal syndrome, was admitted with an acute myocardial infarction complicated by a ventricular tachycardia. He appeared in a terminal state at the time of admission and received sedation and intravenous aminophyllin with no favorable effect. He was not seen in consultation and received no quinidine. Postmortem examination revealed extensive coronary artery disease of the atherosclerotic type. The left circumflex branch was the only vessel which showed some degree of patency. There was a fresh thrombus in the anterior descending branch of the left coronary artery with a fairly large area of hemorrhagic infarction of the anterolateral portion of the left ventricle. There were marked fibrotic changes throughout the entire myocardium of the left ventricle.

Case 2. A 48 year old farmer was admitted October 5, 1942, because of genitourinary difficulty, including hematuria and the passage of gravel. A day prior to admission he had pain in the right costovertebral region. He had suffered with precordial pain associated with exertion for a number of years, but his electrocardiogram had always been within normal limits. He was a known hypertensive, but his heart

Case No.	Age	Digitalis	Underlying Heart Disease	Hypertension	Quinidine Dosage until Cessation of Arrhythmia	Ventricular Rate at Onset	QRS Interval	Congestive Failure	Total Duration of Attack	Anginal Syndrome	Toxicity	Remarks
I	50	No	Anterior wall infarction	No	Untreated	180	0.17	No	Unknown	Yes	None	
II	48	No	None demonstrated	Yes	Untreated	200	0.14	No	Less than 24 hours	No	None	T wave inversion
III	47	No	Anterior wall infarction	Yes	114 grains in 55 hours	170	0.11	Yes	55 hours	No	None	Coupling due to ventricular premature contraction
IV	49	No	Posterior wall infarction	Yes	24 grains in 24 hours	125	0.12	No	Less than 24 hours	Yes	None	2 : 1 AV block
V	46	No	Anterior wall infarction	No	120 grains in 4½ days	160	0.18	No	4½ days	No	None	
VI	51	Yes 8 c.u. in 4 days	Anterior wall infarction	Yes	48 grains in 12 hours	200	?	Yes (Left sided)	12 hours	No	None	Died
VII	59	Yes after vent. tachy.	Coronary arteriosclerosis and hypertension heart disease	Yes	525 grains in 9 days	200	0.13	Yes	9 days	No	Diarrhea and vomiting	AV Dissociation →Nodal rhythm →Reg. sinus rhythm
VIII	60	Yes after vent. tachy.	Coronary arteriosclerosis and hypertension heart disease	Yes	72 grains in 2 days	200	0.13	Yes	14–16 days	No	Diarrhea and vomiting	AV Dissociation →Reg. sinus rhythm
IX	46	No	Coronary disease	No	174 grains in 3 days	216	0.16	No	6 days	No	None	T wave inversion
X	54	No	Coronary arteriosclerosis and hypertension heart disease	No	24 grains in 7 hours	182	0.16	No	7 hours	No	None	A.F.—Lead I RSR—Lead II Vent. tachy. Lead III

was not enlarged. There were no complaints with reference to his cardiovascular system at the time of admission.

His ventricular rate was 200 per minute and regular, not being altered by carotid sinus pressure. The blood pressure was 112 mm. Hg systolic and 96 mm. diastolic; the heart was within normal limits as to size. There was no evidence of congestive heart failure. There was some peripheral and retinal sclerosis.

Electrocardiogram revealed a ventricular tachycardia. He was sedated with morphine and placed on quinidine in doses of three grains four times daily. However, the tachycardia ceased spontaneously prior to the administration of the drug, having persisted for less than 24 hours. There was no clinical or electrocardiographic evidence of myocardial infarction, although at one time a left lateral wall infarct was hypothecated.

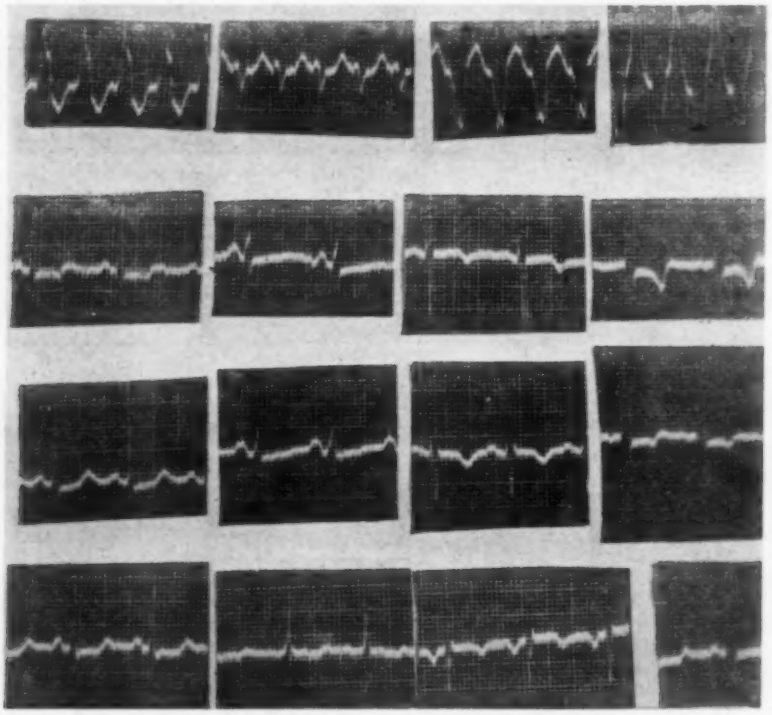

FIG. 2. *Case 2.* Ventricular tachycardia, rate about 200 per minute. Note the very unusual and rather persistent T-wave changes in Lead IV–F and to a lesser degree in Lead I. These changes occurred in the absence of quinidine administration and tended toward reversal in a period of nine days. (From the author's case published in the *Journal of Laboratory and Clinical Medicine,* June 1944.)

Comment. This case reveals the spontaneous termination of the arrhythmia under sedation. It is interesting in that it exhibited rather persistent T-wave inversion in Lead IV–F, and lesser changes in Lead I following the paroxysm. These changes reverted toward normal in a period of nine days. It shows that persistent wave inversion in multiple leads following bouts of tachycardia may occur and are not necessarily of ominous prognostic import. This case was reported in greater detail.[12]

Case 3. A 47 year old white farmer was admitted December 22, 1943, in a condition which did not permit adequate anamnesis. He was a known hypertensive and

admitted increasingly severe exertional dyspnea over a period of three years prior to admission which finally necessitated bed rest three weeks immediately preceding admission. Examination revealed an acutely ill white male, dyspneic, and orthopneic. The neck veins were distended, the heart was enlarged, and the liver was palpated two centimeters below the right costal cage. The heart sounds were poor, A_2 was ac-

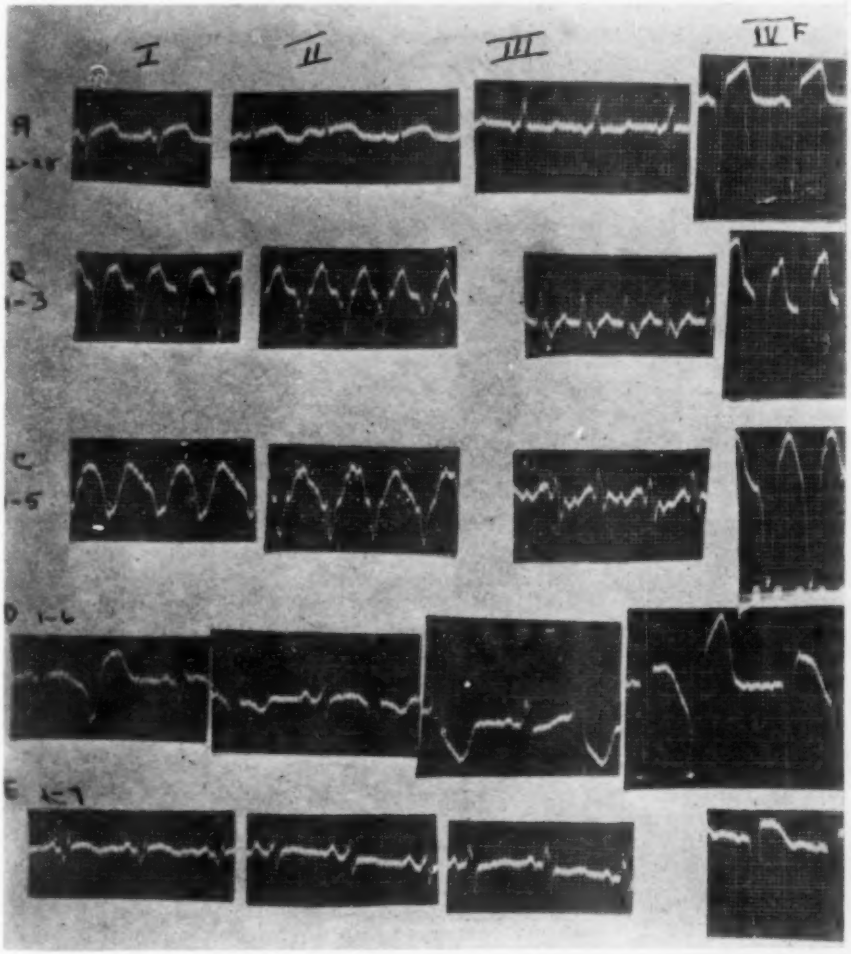

FIG. 3. *Case 3.* These tracings represent an anterior wall infarction complicated by a ventricular tachycardia. The gradual widening of the QRS complexes and the replacement of the ventricular rhythm by a sinus mechanism with coupling are the interesting features of this series.

centuated and the blood pressure was 176 mm. Hg systolic and 114 mm. diastolic. There were dullness and medium sized moist râles over the right base posteriorly.

A diagnosis was made of hypertensive and coronary arteriosclerotic heart disease with congestive failure and hypostatic pneumonia, right lower lobe. The temperature reached 102.4° F. The pulse rate rose to 130 on the day following admission and then both slowly returned toward normal over a period of 10 days. The white blood cell count was 18,000, with 86 per cent polymorphonuclear leukocytes. He was placed

on sulfadiazine and showed slight but definite improvement. However, the heart sounds continued to be extremely poor. On December 28 the patient was able to give a more detailed history and it was ascertained that he had moderately severe retrosternal pain immediately prior to admission. With this information and in view of his clinical course, it was believed that the patient probably had a myocardial infarction. This contention was supported by the electrocardiogram (A) which revealed an anterior wall infarction.

He continued critically ill with an ashen gray cyanosis, relatively afebrile, and with a pulse rate ranging between 80 and 100 per minute until 8:45 a.m. January 3, 1944, at which time his ventricular rate was 170 per minute and quite regular. It did not respond to carotid sinus or ocular pressure. The blood pressure fell precipitously. The clinical impression of ventricular tachycardia was confirmed by electrocardiography (B).

He was given three grains of quinidine immediately and 12 grains three hours later, followed by six grains at four hour intervals. He appeared in extremis. On January 4 the rate was essentially unchanged and the quinidine was increased to nine grains every three hours day and night. This was augmented with potassium chloride, grains 15, three times daily. Oxygen therapy was necessary at this time as well. On January 5, he was given 12 grains at 10:30 a.m. and 12 grains at 1:30 p.m. The electrocardiogram revealed continuation of the arrhythmia (C). By this time the QRS complexes were definitely wider and measured approximately 0.18 second as compared to 0.11 second on the original tracing. No signs of quinidine toxicity were noted clinically. At 4:30 p.m. on the fifth, the ventricular rate was 100 per minute, with definite coupling. The electrocardiogram (D) revealed reëstablishment of the sinus mechanism with regularly recurring ventricular premature contractions following every conducted ventricular beat. By this time the patient received a total of 114 grains of quinidine over a period of less than two and a half days. By January 7 the extrasystoles had disappeared and further changes in the evolution of the infarction may be seen on tracing E.

Quinidine intake was gradually reduced but continued in smaller doses for a 10 day period. Recovery was uneventful.

Summary. Myocardial infarction in a known hypertensive and coronary arteriosclerotic cardiac was complicated by a ventricular tachycardia in the second week of illness. This arrhythmia persisted for a period of approximately 55 hours and terminated after the patient had received 114 grains of quinidine in this period of time. No toxicity attributable to the drug was noted. Following the cessation of the arrhythmia, coupling due to ventricular premature contractions persisted for about 24 hours, and then disappeared. The QRS interval increased to 0.24 second under quinidine therapy.

Case 4. A 49 year old white cotton broker was admitted August 19, 1942, because of a series of attacks of retrosternal oppressive pain for two weeks prior to admission. The most severe and persistent attack occurred four days before admission and lasted for two days. This was accompanied by dyspnea at rest and a fall in blood pressure. He was a known hypertensive, and work-up in 1939 revealed a normal-sized heart, a blood pressure of 170 mm. Hg systolic and 110 mm. diastolic, and an electrocardiogram which showed moderately severe left axis deviation.

At the time of admission his blood pressure was 120 mm. Hg systolic and 70 mm. diastolic. The rhythm was irregular and the sounds were of poor quality. The rate varied from 80 to 120 per minute. It was difficult to evaluate the type of arrhythmia. A tentative diagnosis of coronary occlusion with ventricular extrasystoles and possible A–V block was made. This was confirmed by the electrocardiogram (8–19–42) which showed a very unusual series of tracings. The arrhythmia consisted of a 2:1 A–V block, followed by a persistent paroxysm of ventricular tachycardia with a rate

of approximately 125 per minute. There was one complex, luckily caught in Lead II, which suggested the diagnosis of posterior infarction. No friction rub developed. The sedimentation rate was 100 mm. per hour. The patient was critically ill.

He was placed on quinidine sulphate, grains six, three times daily, and this dosage was continued for 11 days. On August 20 the electrocardiogram (A) showed a sinus

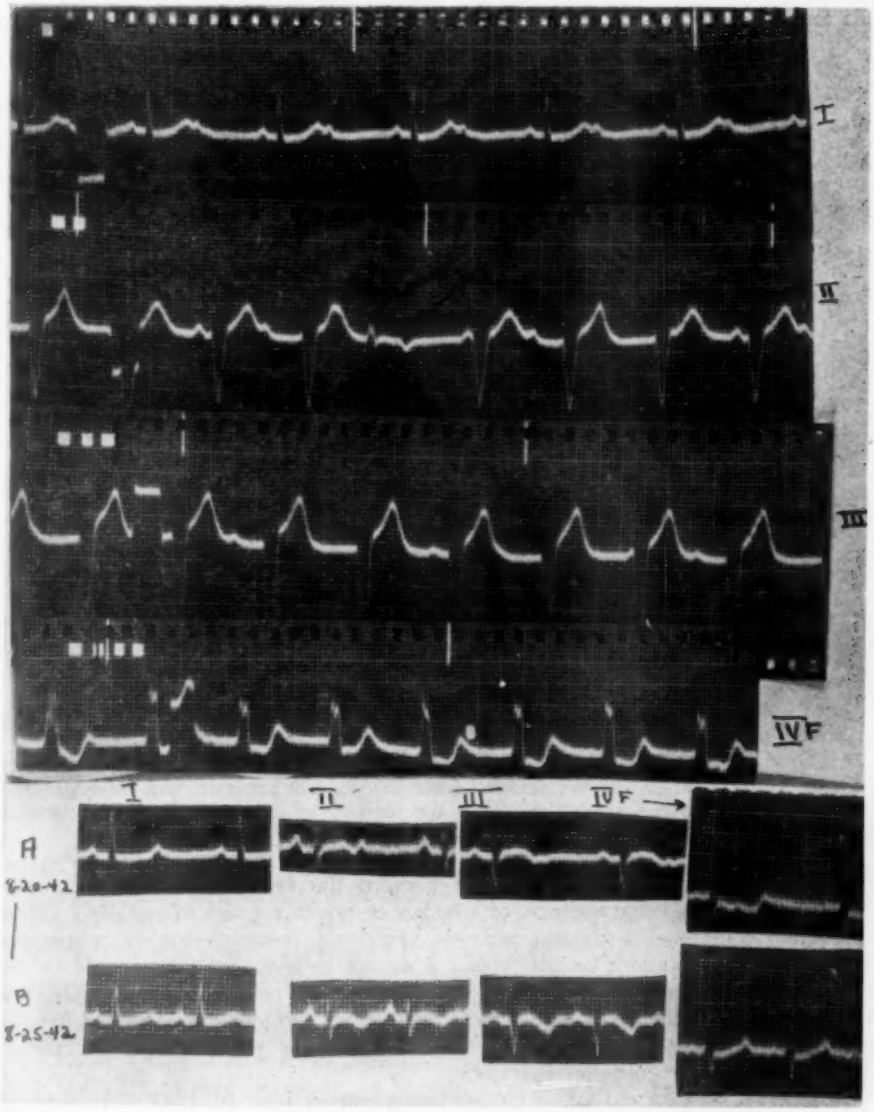

FIG. 4. *Case 4.* A very unusual and interesting series of tracings. Lead I shows a 2:1 A–V block. Lead II shows runs of ventricular beats of bizarre configuration. There is one complex that suggested a diagnosis of infarction in this lead. This was proved by the subsequent tracings and the clinical course of the patient. Leads III and IV in the tracing dated 8–19–42 show the continuation of the abnormal rhythm. The rate was unusually slow. It is felt, however, that the tracing indicates a ventricular tachycardia because of the ectopic origin of the impulse in the "shower" of the ventricular systoles. Note the striking changes when the normal sinus rhythm supervenes in the subsequent tracings.

rhythm with a 2:1 block and confirmation of the posterior wall infarction. Notwithstanding the 2:1 block, quinidine therapy was continued and on August 25 electrocardiogram (B) revealed a normal sinus mechanism with a 1:1 rhythm. His recovery from then on was uneventful.

Summary. A 49 year old known hypertensive male was admitted with a posterior wall infarction of at least a few days' duration, complicated by a ventricular tachycardia and also a 2:1 A–V block. Quinidine in doses of 18 grains daily terminated

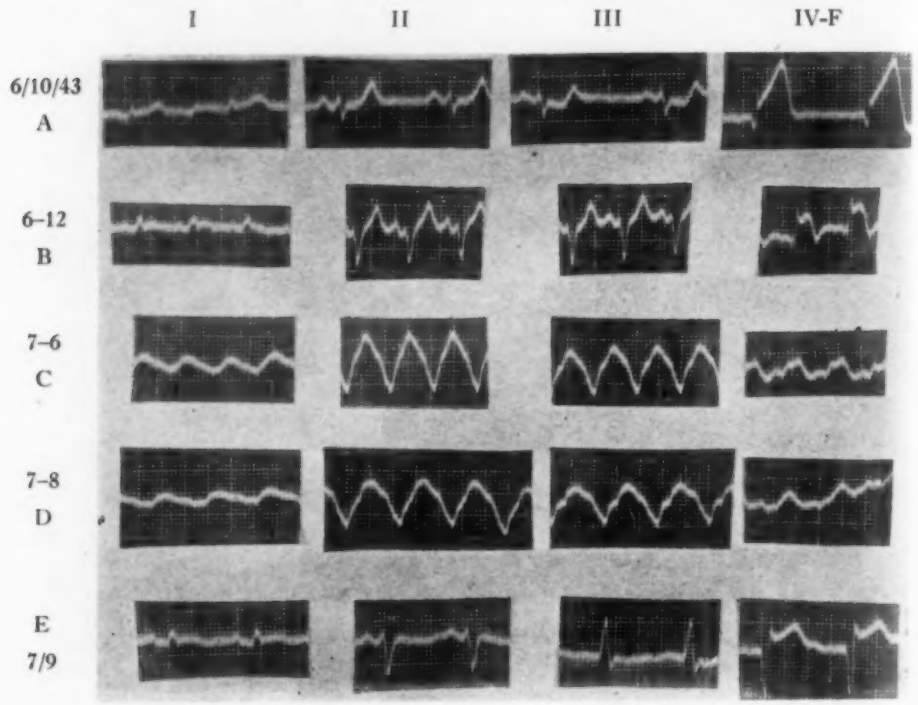

FIG. 5. *Case 5.* See text for details. This is a case of anterior wall infarction complicated by a ventricular tachycardia. Note the marked widening of the QRS complexes under quinidine therapy, as well as the reduction in the rate of the ectopic rhythm.

the ventricular tachycardia and did not prevent the return of the normal sinus mechanism. The academic question of whether or not this series of rapidly recurring bizarre QRS complexes represents multiple ventricular escape beats, or a true ventricular tachycardia, cannot be answered. I do not believe that they should be considered as separate and distinct entities. Whether or not spontaneous subsidence of the ventricular tachycardia would have taken place without quinidine is anybody's guess. No ventricular extrasystoles recurred following the cessation of the arrhythmia, while under quinidine therapy.

Case 5. A 46 year old white lawyer was admitted June 10, 1942, with a history of severe squeezing retrosternal pain accompanied by shortness of breath. The pain radiated down both arms and had been present for one and a half hours at the time of admission. The past history was not relevant. Examination revealed a moderately thin white male, perspiring profusely and in obvious pain. There was slight cyanosis of the nail beds. The heart was not enlarged. There was regular sinus rhythm. The first sound over the apex was barely audible. There was no friction rub, no thrills or

murmurs. Blood pressure was 110 mm. Hg systolic and 74 mm. diastolic. A clinical diagnosis of myocardial infarction was supported by the electrocardiogram, which showed an acute anterior wall occlusion with low voltage (A).

The patient was given intravenous aminophyllin and morphine. His pulse rose steadily and reached 140 per minute on June 12, and then slowly fell to a rate of 90 to 100. There were no ventricular extrasystoles present. Electrocardiogram (B) showed further changes in the evolution of the anterior wall infarction and a more rapid sinus rate. Oxygen was administered with favorable results, the patient becoming more comfortable and less dyspneic. On June 26, he incurred an upper respiratory infection accompanied by a slight temperature rise. This subsided rapidly. On June 29 he again complained of pain in both shoulders; his temperature rose slightly and remained at a level of 100 to 101° F. until July 13, 1944.

On July 5, 1944, at 10:00 a.m., he was found in shock. The pulse rate was 166 per minute and barely perceptible. The blood pressure was unobtainable. There was no pain. The rapid rate did not respond to carotid sinus pressure or ocular pressure. He was sedated and started on quinidine therapy in gradually increasing doses, receiving 30 grains by July 6. Electrocardiogram (C) revealed a ventricular tachycardia with a rate of 160 per minute. The QRS duration was .18 second. The arrhythmia continued and quinidine was increased to 12 grains four times daily. By June 8 his ventricular rate had slowed to 140 per minute and the QRS interval increased to .20 second (D).

The heart became larger clinically, and basal râles soon became apparent. No digitalis, however, was administered. He appeared relatively comfortable, and remained slightly febrile. Quinidine was continued in doses of 12 grains every six hours, and on June 9 his rate dropped to 80 per minute and he experienced an abrupt change for the better in his condition. The electrocardiogram (E) revealed a regular sinus rhythm with other relevant ST and T-wave changes. Quinidine was gradually reduced during the remainder of his hospital stay, but the appearance of frequent extrasystoles necessitated increase in dosage, so that a dose of nine grains four times daily was required to suppress the ventricular premature contractions. His recovery from then on was uneventful.

Summary. A 46 year old white male entered the hospital with an acute anterior wall occlusion which was complicated by a ventricular tachycardia in the fourth week of his illness. He appeared in a terminal state on many occasions. Quinidine in moderately large doses was administered. The arrhythmia persisted for four and a half days. One hundred and twenty grains of quinidine were given before the arrhythmia ceased; the highest daily dosage was 48 grains. It was necessary to continue the administration of quinidine during the remainder of his hospital stay because of the appearance of ventricular premature contractions. Nine grains four times daily appeared to be the optimal dosage.

In retrospect, it is believed that quinidine was not given in sufficiently large doses and the intervals of administration were too long, but this is a difficult point to prove.

Case 6. A 51 year old white male, a known hypertensive of moderate severity, was admitted May 23, 1943, with a history of severe retrosternal oppression, radiating to both shoulders. This began May 18, 1943, and recurred three times in four days. The last attack occurred on the day prior to admission and persisted, although of lesser severity, up to the time of admission. On admission he appeared critically ill and was in mild shock. The blood pressure was 86 mm. Hg systolic and 60 mm. diastolic. The heart was not enlarged. The sounds were extremely poor in quality. There was no gallop or pericardial friction rub. There was no evidence of congestive failure. The peripheral and retinal vessels were sclerotic. A diagnosis of recent myocardial infarction was confirmed by electrocardiography (A). The rhythm was regular sinus and the infarction was on the anterior wall.

Intravenous aminophyllin, together with sedation and oxygen, were administered. Singultus was extremely troublesome and did not respond to the usual modes of therapy. He merged slowly into left-sided failure and it was believed advisable to digitalize the patient cautiously. On May 29, one and one half grains of digitalis were given twice daily, and this was continued, with little change in his condition. His hiccups stopped on June 1, at which time his temperature and pulse rate returned to normal. There were no extrasystoles. The sounds continued to remain extremely poor. The blood pressure was 96 mm. Hg systolic and 62 mm. diastolic. On June 2, at 2:20 p.m., his ventricular rate rose suddenly to 200 per minute. A diagnosis of ventricular tachycardia was confirmed by electrocardiography. After a test dose of three grains of quinidine he was given 15 grains, followed by six grains every two hours. The patient died at 2:40 a.m. June 3, 1944. There was equivocal evidence of embolic occlusion of the right femoral artery, just prior to death. He received 48 grains of quinidine in a little less than 12 hours.

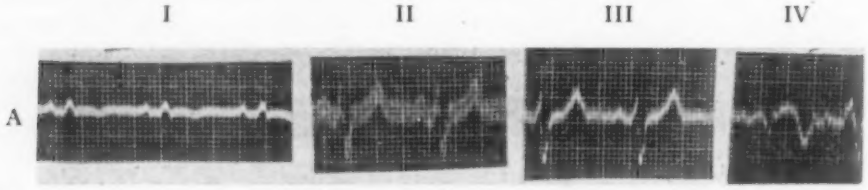

FIG. 6. *Case 6.* The anterior wall infarction is seen. The electrocardiogram showing the ventricular tachycardia is not available.

Comment. Ventricular tachycardia complicating an anterior wall infarction ended fatally approximately 12 hours after its onset. During this time 48 grains of quinidine had been administered. This patient received very small doses of digitalis for a period of four days prior to death, eight cat units having been administered in four days. It appears unlikely that digitalis in the doses given played any etiological part in this arrhythmia.

Unfortunately, the electrocardiogram showing the ventricular tachycardia in this case is not available.

Case 7. A 59 year old negro male was admitted May 24, 1943, acutely ill, mentally confused, and in severe congestive failure. The pulse was not perceptible and no blood pressure reading could be obtained. There was definite clinical evidence of forward failure (shock) as well as generalized anasarca, ascites, dyspnea and orthopnea. The only history obtained from his family was the fact that patient's blood pressure had been high for an unknown period. The heart rate was rapid and regular, approximately 200 per minute. The heart sounds were poor. The heart was enlarged.

He was placed on digitalis and sedated prior to cardiac consultation. He was seen in consultation on May 25 and a diagnosis of ventricular tachycardia was confirmed by electrocardiograph (A). He was placed on 9 grains of quinidine orally every three hours, day and night, and by May 29 he had received a total of 315 grains. By this time the ventricular rate had slowed to 118–120 per minute, and the patient felt somewhat better, although he remained in severe congestive failure. Electrocardiogram (B) revealed persistence of the ectopic rhythm with a rate of 118 per minute; the QRS interval had widened to almost 0.18 second. On May 30 his quinidine intake had been discontinued by the ward surgeon so that he received only 18 grains for the entire 24-hour period. Electrocardiogram of May 31 again revealed a rapid rate (205 per minute) with a decrease in QRS conduction time (C). Quinidine was then increased to 12 grains every three hours on May 31, augmented with

potassium citrate in small doses. This dosage was continued through June 1, so that he received 132 grains on May 31 and June 1, and 60 grains more on June 2. At 3:00 p.m. on June 2 his ventricular rate was 60 per minute. Electrocardiogram (D) revealed a sinus mechanism with a complete A–V dissociation. The total amount of quinidine administered in nine days was 525 grains. Signs of toxicity by this time included a moderately severe diarrhea, vomiting, and abdominal pain. From then on quinidine was administered in 6 grain doses, four times daily, until June 15 and then reduced to three grains, three times daily. Other measures to combat the severe congestive failure including mercurial diuretics, ammonium chloride, and sedation

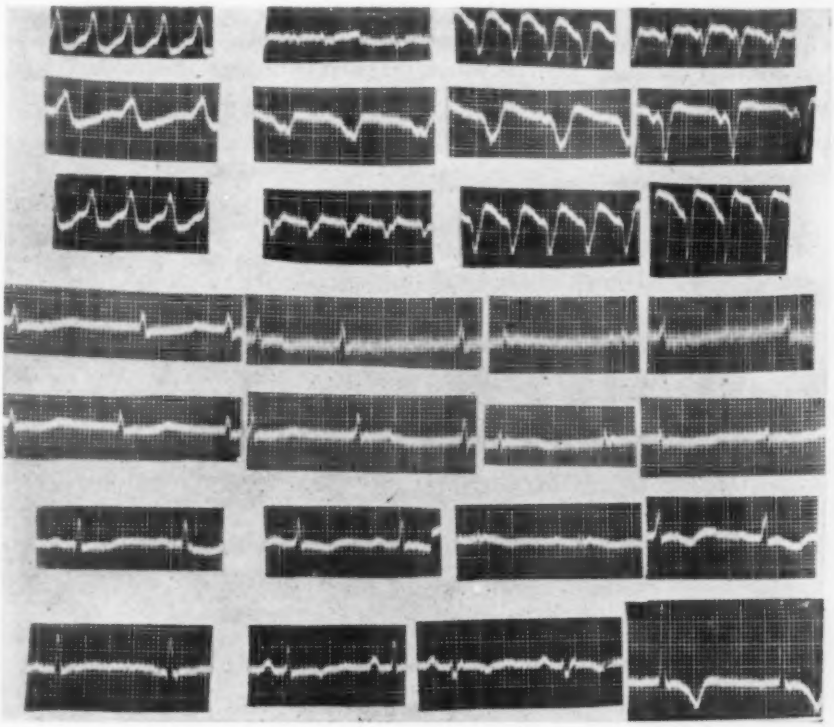

FIG. 7. *Case 7.* See text for details. Note the transition stage of complete A–V block in tracings D and E. In tracing B note the marked slowing, followed by the return to a more rapid rate as seen in tracing C. The latter record was taken shortly after the quinidine was temporarily reduced. The reëstablishment of the normal sinus mechanism is seen in the last record.

eventually enabled this patient to become ambulant. He was discharged with maximum benefit with a moderately severe diminution in his cardiac reserve. A probable nodal rhythm is seen on tracing E, and regular sinus mechanisms are seen on tracings F and G. Note the deep T-wave inversion in Lead IV–F. During his hospital stay he had received a total of 922 grains of quinidine, 525 of which were given prior to the termination of the ectopic rhythm.

Comment. A 59 year old negro with hypertensive and coronary arteriosclerotic cardiac disease was admitted in severe congestive heart failure with a ventricular tachycardia of unknown, but probably extended duration. Prior to consultation he was placed on digitalis, but later treated with massive doses of quinidine sulphate. In a period of nine days 525 grains were administered orally after which the tachy-

cardia gave way to a slow rate with complete A–V dissociation and then to a normal sinus mechanism. Signs of toxicity included vomiting, foul diarrhea, and abdominal pain, although the patient had vomited persistently prior to the introduction of quinidine. The patient was finally discharged able to get about, albeit with a diminished myocardial reserve.

Case 8 was again admitted June 16, 1944, in severe failure, with a history of rapid heart action for two weeks prior to admission. He stated that he had done quite well since his discharge, and it could not be ascertained whether or not he had been taking digitalis. With our experience with negroes in this section of the country it seemed highly improbable that he had been taking the drug. The rate was 200 per minute, the sounds poor, the blood pressure unobtainable. Again, forward failure was engrafted upon severe congestive failure. There was no response to ocular or carotid sinus pressure. Vomiting was persistent. The patient was uremic and relatively anuric.

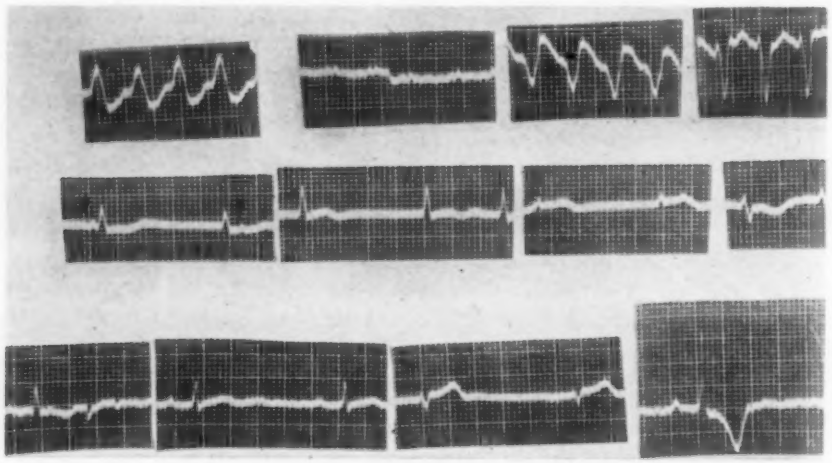

FIG. 8. *Case 8.* See text for details. Again the same sequence from ventricular tachycardia to complete A–V block to normal sinus rhythm is seen.

Quinidine therapy was instituted on the day of admission, in doses of three grains every two hours, day and night; the dose was doubled on the seventeenth. On the seventeenth, electrocardiogram revealed that the arrhythmia had broken; again complete A–V dissociation with a slow idioventricular rhythm was exhibited (B). Digitalis, in conjunction with quinidine, was administered, in addition to hypertonic glucose, intravenously, and mercurial diuretics. With this therapy his urinary output improved rapidly and signs of congestive failure diminished. The urinary output exceeded 6000 c.c. daily and the non-protein nitrogen fell rapidly. Final tracing (C) dated June 27, 1944, revealed a normal sinus mechanism. The patient was discharged feeling well, and ambulant, with minimal edema. Seventy-two grains of quinidine over a two day period were required to terminate the arrhythmia.

Comment. A second paroxysm of ventricular tachycardia in a 60 year old negro male, with hypertensive and arteriosclerotic heart disease, responded favorably to large doses of quinidine given frequently by the oral route. The duration of the attack was probably 14 to 16 days. There was no clinical or laboratory evidence of myocardial infarction. Deep T-wave inversion in Lead IV–F similar to that seen on the prior admission occurred. Again, the interesting sequence of events included the

intermediate stage of complete A–V dissociation. This was not considered a contraindication to either digitalis or quinidine administration. The amount of quinidine required to terminate the arrhythmia was decidedly less than that needed in the prior attack, although the short interval of administration was probably an important factor in the favorable outcome.

Case 9. A 46 year old white male had known coronary artery disease. He was known to have had attacks of paroxysmal rapid heart action in the past which, on at least one occasion, was proved to be ventricular in origin. He was not a known hypertensive. He was admitted September 14, 1942, with a history of an abrupt onset of rapid heart action 48 hours prior to admission. Attempts at terminating the ectopic rhythm by his local physician included the use of quinine and digitalis, but to no avail.

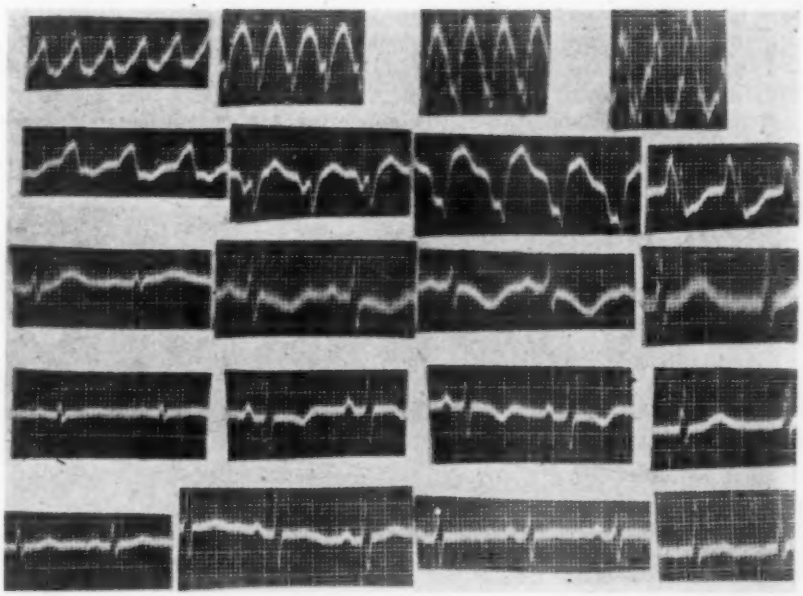

FIG. 9. *Case 9.* Ventricular tachycardia rate slightly above 200 per minute. Note the widening of the QRS complexes following quinidine therapy with a slowing of the ectopic ventricular rate. When sinus rhythm was reëstablished the T-waves became inverted in Leads II and III. This persisted for approximately one month and occurred in the absence of Q-waves and reciprocal ST changes (from the author's case published in the *Journal of Laboratory and Clinical Medicine*, June 1944).

At the time of admission examination revealed a regular ventricular rate of 216 per minute. The pulses were barely perceptible; the blood pressure could not be obtained; the sounds were of fair quality. No murmurs were audible. The heart was not enlarged. He was in shock. The rate could not be altered by carotid sinus or orbital pressure. There was moderate peripheral and retinal sclerosis. The patient was placed on quinidine sulphate, grains six, four times daily. On September 15, 1942, there was no change in rate or rhythm, six grains of quinidine every two hours were administered, and the patient was sedated with morphine. By 4:45 p.m. on September 15, 1942, he had had 48 grains of quinidine. This dosage was continued through midnight September 15, 1942, and again at 7:30 a.m. September 16, 1942. By the sixteenth his rate was reduced to 112 per minute and was regular. Electrocardiogram (see figure) revealed persistence of the ectopic rhythm, with a rate of 132

per minute. The QRS interval increased considerably and measured 0.19 second as compared to 0.16 second on the original tracing. On the morning of the eighteenth his ectopic rhythm had given way to a regular sinus one, with a rate of 84 per minute. By this time he had received 174 grains of quinidine in three days. Six-grain doses every four hours were continued day and night for two days and then the dosage was gradually reduced. His recovery was uneventful.

Comment. A case of ventricular tachycardia of six days' duration was terminated abruptly with the aid of fairly large doses of quinidine sulphate given orally. Six grains every two hours was the largest dose administered to this patient. No toxic effects were observed clinically. The electrocardiogram revealed widening of the QRS complexes with a slowing of the rate, and then return to normal sinus rhythm. Most interesting was the inversion of the T-waves seen in Leads II and III. These inversions, unaccompanied by Q-waves or reciprocal S–T changes, persisted about one month and then returned to their original upright configuration. Whether they indicate "myocardial fatigue" or manifest coronary insufficiency brought on by the tachycardia is not known. Nevertheless, it would appear that they are not necessarily of ominous prognostic importance. This case was reported in detail elsewhere.[12]

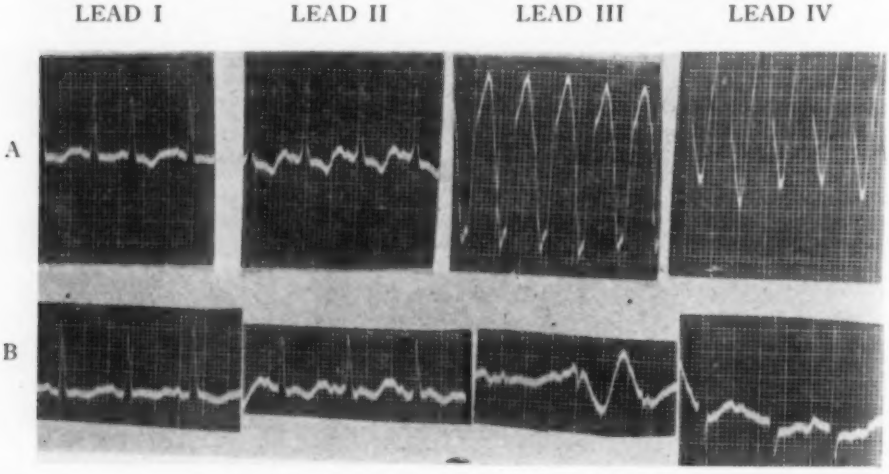

FIG. 10. *Case 10.* See text.

Case 10. A 54 year old negro male had been hospitalized for a period of two years because of severe diabetes and multiple sclerosis. He was known to have had hypertensive and coronary arteriosclerotic cardiac disease, his blood pressure having been moderately elevated. On October 22, 1944 his diabetes became exceedingly difficult to control, the patient became drowsy and his urine showed a marked glycosuria. His insulin was increased and other treatment was directed toward his impending coma.

On October 26 his ventricular rate suddenly rose to 180 per minute, the patient went into shock, and appeared in a terminal state. Cheyne-Stokes respirations were present. Electrocardiogram (A) revealed an interesting combination of arrhythmias, Lead I showing an auricular fibrillation, Lead II a regular sinus rhythm with a PR interval of .09 second and Leads III and IV revealed a ventricular tachycardia with a rate of 182 per minute.

With this tracing confirming the clinical impression of ventricular tachycardia, the patient was given 15 grains of quinidine orally and then 9 grains every three

hours day and night. This dose was continued throughout the night, during which time the arrhythmia ceased. The dosage was subsequently reduced to 3 grains every four hours. Electrocardiogram (B) taken on October 27 revealed a return to a regular sinus mechanism with a few ventricular premature contractions. These subsequently disappeared.

Summary. A 54 year old negro male with diabetes and known hypertensive and coronary disease developed a ventricular tachycardia during a period of uncontrolled hyperglycemia and possible acidosis. Quinidine in large doses succeeded in terminating the arrhythmia within a period of seven hours, after a total of 24 grains of the drug in the same period of time.

Discussion

The ominous prognostic significance of paroxysmal ventricular tachycardia is universally known. It is felt, however, that the underlying heart disease is the ultimate determiner with respect to the immediate outcome. This is particularly true in cases of recent coronary thrombosis. It is difficult, therefore, to arrive at any reliable mortality statistics with respect to this rhythm. That it is high is well known, and the gravity of this complication following cardiac infarction need not be further discussed. The recovery of seven of the eight treated cases which comprise the body of this report is sufficiently striking to warrant reporting.

In this series the ages ranged from 46 to 60. This is in line with the average age of the veteran of World War I at this time, and does not lend itself to any type of analysis. The arrhythmia complicated infarction in five of the 10 cases. In four of these the infarct was situated on the anterior wall, and in one it was situated on the posterior wall. In one of the 10 cases no underlying heart disease could be demonstrated, whereas coronary disease, alone or associated with hypertension was present in the remainder. Hypertension was present in six, and the anginal syndrome was present in two of the 10 cases. None of the cases gave any history of rheumatic fever and there was no evidence of valvular disease in any of the patients.

The rôle played by digitalis in the causation of this arrhythmia has been stressed by many authors. In Williams and Ellis'[8] series of 36 cases abstracted from the records of the Boston City Hospital, digitalis had been administered in 17. In eight of these there was no apparent question as to the association of the arrhythmia and digitalis. In the other remaining nine cases the amount of digitalis administered was in excess of the theoretic requirement, and no other cause for the attack was apparent. With reference to the cases reported here only one of the 10 had digitalis prior to the onset of the ventricular tachycardia. This patient (case 6) had been given only eight cat units in a period of four days. It would appear highly unlikely that this drug had any causal relationship to the establishment of this ectopic rhythm.

The ventricular rate at the time of the establishment of the arrhythmia varied from 125 to 216 per minute. Definite and unequivocal slowing of the ventricular rate followed the administration of the drug in all cases. As

stated above, widening of the QRS interval was a definite accompaniment of quinidine exhibition, in many cases the prolongation assuming considerable magnitude. There did not appear to be any relationship between the initial rate, the width of the QRS interval, the duration of the attack and the final outcome.

Of the untreated cases, one case (case 2) reverted to a normal sinus mechanism following sedation with morphine. The other one (case 1) died within a few hours after admission, following a massive infarction of the anterior wall of the left ventricle. The remaining eight cases were alive for a sufficient length of time to permit adequate therapy. Of these eight there was only one death (case 6), and this patient died within 12 hours after the exhibition of this arrhythmia, having received 48 grains of quinidine in this period of time. He had clinical evidence of massive infarction of the anterior wall of the left ventricle together with a borderline low voltage electrocardiogram. Whether or not this patient would have died even without the complicating ventricular tachycardia is conjectural. He appeared in extremis prior to the exhibition of this arrhythmia. The remaining three treated infarction cases which recovered appeared just as ill, however.

There did not appear to be any relationship between the amount of quinidine given and the ultimate outcome. The most persistent case required 525 grains over a period of nine days. The least amount given was 24 grains in 24 hours. This was a case of posterior wall infarction, and the arrhythmia was definitely paroxysmal (case 4). The QRS intervals varied, at the onset, between 0.11 and 0.18 second. In the case which was treated and died, the electrocardiogram showing the ectopic rhythm is not available for analysis. The total duration of the arrhythmia, including the time it was present prior to admission, varied between seven hours and 16 days. The longest duration while under treatment was nine days.

The only evidence of quinidine toxicity, in spite of the relatively large doses administered, was persistent diarrhea and vomiting in one case. In view of the critical condition of this patient and because it was felt that the continuation of the tachycardia would eventually kill the patient, the drug was pushed to the limits of the patient. The outcome was successful. Following the cessation of the arrhythmia two of the patients exhibited T-wave inversion in more than one lead. There was no clinical or electrocardiographic evidence of myocardial infarction. That the T-wave inversion was not the result of quinidine therapy has been discussed elsewhere.[12] These changes are depicted in the tracings accompanying cases 2 and 9. In case 3 coupling due to ventricular premature contractions preceded the reëstablishment of the normal sinus mechanism. In case 4 a 2:1 A–V block preceded the sinus mechanism and this conduction defect was not adversely affected by further quinidine administration. The paroxysms in cases 7 and 8 passed through a state of complete A–V dissociation prior to the appearance of a normal sinus rhythm. Quinidine did not prevent the evolution of this sequence.

Summary

1. Ten cases of ventricular tachycardia are reported and discussed from the standpoints of underlying heart disease, causal effects of digitalis, ventricular rates, QRS intervals and the presence of congestive cardiac failure. Digitalis was not causal in the production of the arrhythmia in any of the reported cases. Five of the 10 cases complicated myocardial infarction. In one case no underlying cardiac disease could be demonstrated. In the remaining cases coronary disease, alone, or in association with hypertension was easily established.

2. Eight of the 10 cases were treated with relatively large doses of quinidine. Seven of these cases recovered. Three of these paroxysms complicated myocardial infarctions, and were successfully treated. The only death occurred in a patient who had a massive anterior wall infarction and who appeared in a terminal state even prior to the onset of the arrhythmia.

3. The total amount of quinidine required to terminate the arrhythmia varied greatly from case to case. Large doses were given unhesitatingly with extremely gratifying results. Toxic signs and symptoms were negligible. The QRS interval was disregarded as an index of quinidine toxicity.

4. The recent literature bearing on the subject has been discussed. Relatively few reports dealing with the effect of large doses of quinidine on this arrhythmia have been noticed.

5. From a review of this series, and as a result of the perusal of the sparse recent literature, quinidine in adequate, and massive doses if necessary, is recommended in the treatment of ventricular tachycardia. There does not appear to be any unequivocal evidence that its administration following acute coronary occlusions is in any way detrimental.

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CASE REPORTS

ANEURYSM OF AORTA WITH COMPRESSION OF PULMONARY ARTERY AND LEFT AURICLE *

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Case Report

The patient, a 42 year old Spaniard, was admitted on September 15, 1943, with the chief complaint of dyspnea of six months' duration.

About six months previously the patient caught cold with which he had a stuffy nose, sore throat and cough. He was treated symptomatically by his private physician without improvement and about four months prior to this admission was hospitalized elsewhere for pneumonia. He remained there about one week and then tried to return to work as a grocery clerk, but had to stop because of dyspnea on the slightest exertion, and weakness. Following this, despite rest, he became progressively worse until two days before admission, he was obliged to seek hospitalization. Orthopnea and nocturnal dyspnea had been present for one week. There had never been any edema. He had lost weight steadily, a total of 35 pounds, and his chronic cough of several years' duration had become worse. Sputum was scant, mucoid, never blood streaked. In addition, morning vomiting was often present during the preceding four months, but had become less frequent during the last two months. There also had been some abdominal pain of crampy nature, usually after eating, and relieved by vomiting. The vomitus was greenish and sometimes contained flecks of blood at the end of the vomiting spell. The bowels had been regular, the stools were never tarry and contained no frank blood.

There was a history of having worked for nine years in soft-coal mines. The patient believed his cough started some time during this period, but he had never been dyspneic until six months before admission.

The family history was not significant, except that the patient's father had died of heart disease.

There was a history of syphilis, contracted at the age of 14, which was treated when a secondary rash appeared. He had received intravenous and intramuscular medication over a two months' period. The patient denied ever having had gonorrhea. At the time of his hospitalization for pneumonia, the Kahn reaction had been positive.

Physical Examination on Admission: Temperature 98.6° F. Pulse 100. Respirations 28. Blood pressure 130 mm. Hg systolic and 70 mm. diastolic.

General Appearance: The patient appeared chronically and acutely ill, sitting up in bed, coughing and wheezing. There was mild dyspnea but no orthopnea. Cyanosis of the nail beds was present, but not of the lips.

Head: Extraocular movements were normal. Pupils showed normal reactions. The conjunctivae and fundi were normal. The nose was negative. The tongue was in the mid-line and coated. The pharynx was red and the teeth foul.

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From the First Medical Division, Bellevue Hospital, New York City, Dr. I. Ogden Woodruff, Director.

Neck: The veins were distended, did not pulsate, and filled from above. The trachea was in the mid-line and the thyroid not enlarged.

Heart: The point of maximum impulse was in the fifth space at the mid-clavicular line. The apical sounds were of rather poor quality. P_2 was greater than A_2. The rhythm was regular with a rate of 100. Over the apex, there was a long, blowing systolic murmur and a short presystolic blow, heard with the patient in the left lateral recumbent position. No thrill was palpable.

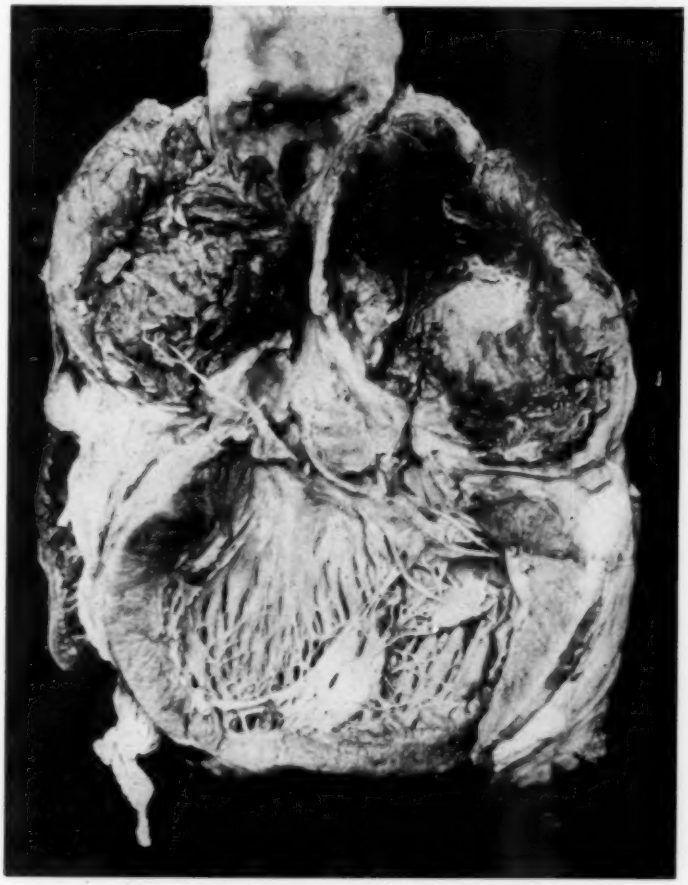

FIG. 1. Left ventricle and aneurysm.

Lungs: There was diminished tactile fremitus over the left lower lobe. Many rhonchi, squeaks and wheezes were present, especially when the patient had paroxysms of coughing which was wheezing in character.

Abdomen: The liver was tender and enlarged, three fingers below the costal margin. The spleen was not palpated and no masses were present.

Extremities: Cyanosis of the nail beds was present. Clubbing and edema were absent.

Reflexes: Were normal.

Rectal: There were no tenderness, masses or enlargement of the prostate.

Course: The temperature ranged between 98° and 101° F., the pulse between 80 and 128, the respirations between 18 and 24. The patient became markedly dyspneic,

orthopneic and cyanotic, despite treatment with morphine, aminophylline, mercupurin, digitalis and low salt diet. The neck veins became more distended, and the liver enlarged further and some observers thought that expansile pulsation was present. No evidence of moisture in the lungs was ever noted. The cardiac signs varied somewhat with different observers. All, after the third day, heard a diastolic murmur at the base and along the left sternal border; most heard a diastolic murmur at the apex also, as well as a systolic murmur. The majority thought that the second pul-

FIG. 2. Right ventricle and pulmonary artery with the area of indentation and erosion caused by aneurysm.

monic sound was accentuated and louder than the second aortic sound. The pulse was not Corrigan in type. The course was rapidly downward and he died on September 23, eight days after admission. No râles were heard in the lungs until pulmonary edema appeared in the final few hours.

An electrocardiogram revealed a sinus rhythm with a tachycardia and a delayed A–V conduction time (prolonged P–R interval).

A roentgenogram of the chest was interpreted by the roentgenological department as follows: "Heart enlarged in all diameters; widening of the supracardiac aorta. Configuration was that of mitral disease."

Fluoroscopic examination by one of the attending staff revealed enlargement of the left auricle and left ventricle, and apparent enlargement of the conus.

The venous pressure was 260 mm. water. Circulation time with decholin, 90 seconds, with ether 60 seconds.

Urinalyses were normal, except for two-plus albumin. The Wassermann reaction was anticomplementary and the Kahn four plus. The blood count was normal except for a mild hypochromic anemia. The erythrocyte sedimentation rate was 9 mm. per hour.

FIG. 3. Left auricle.

Clinical Diagnosis: Syphilitic heart disease with aortic insufficiency and aneurysm of ascending aorta; rheumatic heart disease with aortic insufficiency and mitral stenosis and insufficiency.

Autopsy Report (Drs. Harvey and Spain): The body was that of a moderately well developed, well nourished, white male, 42 years of age. The scalp hair was grayish-black, fine and plentiful. The axillary, chest and pubic hair were of normal masculine distribution. The skin was normal in texture and turgor. There was marked cyanosis of the face, neck and nailbeds. The pupils were regular in outline and equal. The conjunctivae were slightly injected but otherwise showed no changes.

There were no changes referable to the ears, external nares, or mouth. The trachea was in the mid-line. The thyroid was not palpable. No lymph nodes were felt in the axillary, cervical or inguinal regions. The chest was symmetrical. The abdomen was scaphoid in contour. The genitalia were normal in size, shape and appearance. There was no edema or clubbing of the upper and lower extremities. There was a gaping wound in the left antecubital fossa which measured 2 cm. in length (phlebotomy wound).

The usual Y-shaped incision was made. The subcutaneous fat was slightly reduced in amount. The red muscles were moderately well developed. When the abdomen was opened the peritoneum was seen to be smooth and glistening. There were 1,000 c.c. of clear yellow fluid in the peritoneal cavity. The liver extended 5 cm. below the right costal margin. The left dome of the diaphragm was at the fifth interspace; the right dome was at the fourth rib.

Both pleural cavities were dry. The left pleural cavity was free of adhesions. There were many firm fibrous adhesions binding the right lung to the chest wall. It was necessary to remove this lung extrapleurally as the adhesions could not be broken.

Heart: On section of the right heart the endocardium was seen to be smooth and glistening. There was a moderately large thrombus occupying the right auricular appendage. The right auricle was free of thrombi and was not dilated. The foramen ovale was closed. The tricuspid valve cusps were thin and delicate and the chordae tendineae were neither shortened nor fused. There was neither fusion nor separation of the pulmonic valve cusps at the commissures and the cusps showed no changes. The right ventricular wall measured 7 mm. The columnae carneae were slightly flattened. The myocardium was uniformly light brown in color.

On section of the left heart the endocardium was seen to be smooth and glistening except for two plaques in the left auricle. The larger plaque measured 3 by 2 cm., the smaller measured 1 cm. in its greatest diameter. These areas were covered by friable shaggy masses which were more or less firmly attached to the endocardium. The mitral valve cusps were thin and delicate as were the chordae tendineae. The latter were neither shortened nor fused. The left ventricular wall measured 1.4 cm. The myocardium was uniformly light tan in color. The aortic valve cusps were thin and delicate. There was a questionable separation of one commissure; however, there was slight fusion of the other two cusps at their junction. Just above the valves there was a large saccular aneurysm of the aorta. This aneurysm bulged anteriorly and laterally. Its walls were thick, and the endothelial surface was covered by a shaggy friable light brown material. A large thrombus occupied the lumen of the aneurysm. The lumen of the aorta ran posteriorly to the aneurysm. The aneurysm was adherent to the posterior surface of the pulmonary artery and markedly diminished its lumen. At the point of greatest narrowing of the pulmonary artery (4 cm. above the valve), there was a large irregular plaque of friable reddish-brown material which was firmly adherent to the intima. This plaque measured 3 by 0.5 cm. In a similar fashion, but to a less extent, the aneurysm was adherent to and bulged into the left auricle.

There was partial stenosis of the coronary ostia. This was more marked on the left than on the right. In the first portion of the ascending aorta, there were numerous fine longitudinal wrinklings of the intima. The arch and thoracic portions of the aorta showed numerous light yellowish-gray plaques on the intimal surface. There were, in addition, minimal arteriosclerotic plaques throughout the entire course of the aorta. The renal arteries showed no changes.

Lungs: The lungs together weighed 1,100 gm. The pleural surfaces of the lungs were smooth, grayish-black in color and glistening. On section the parenchyma of the left lung, which was cottony to touch and crepitant throughout, was seen to be uniformly grayish-black in color. The pleural surface of the right lung was shaggy in appearance and yellowish-black in color. The parenchyma was cottony to touch,

crepitant throughout, and uniformly grayish-black in color. There was neither exudate nor fluid in the parenchyma or bronchioles of either lung.

The tracheobronchial lymph nodes were slightly enlarged, black and firm. On section a uniformly black surface was seen.

Liver: The liver weighed 1,450 gm. The capsule was smooth, glistening and light gray in color except that portion of it which covered the lower pole of the right lobe. Here the capsule was thickened, opaque and yellowish-gray in color. On section the

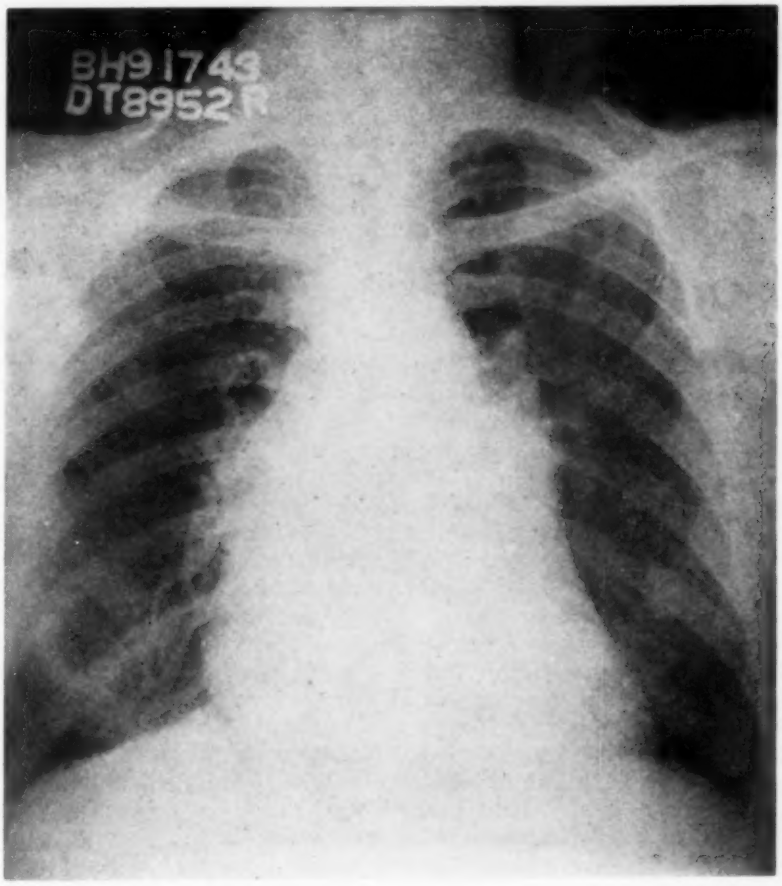

FIG. 4. Roentgenogram of chest.

moderately firm parenchyma was seen to be yellowish-red in color. It had a "nutmeg" appearance and the lobular architecture was accentuated. The portal vein, hepatic artery, hepatic, cystic and common bile ducts showed no changes.

Gall-Bladder: The thin walled gall-bladder contained 80 c.c. of a thick dark green viscid bile. The dark green mucosa was velvety in appearance. No stones were present in the biliary tract.

Pancreas: The firm yellowish-white pancreas was normal in size and shape. On section the lobular architecture was seen to be well preserved.

Spleen: The spleen weighed 120 gm. The gray, glistening capsule was slightly wrinkled. On section the Malpighian corpuscles stood out clearly as did the trabeculae against the background of the deep reddish-purple firm pulp.

Adrenals: The adrenals were normal in size, shape and consistency. On section the yellow cortex and grayish-brown medulla were seen to be normal in width and appearance.

Kidneys: Each kidney weighed 200 gm. The capsule of the right kidney stripped with ease, revealing a smooth, reddish-brown cortex. On section the cortex was seen to be normal in width and was easily demarcated from the medullary pyramids which were of the same color. The open pelvis, calyces and ureter were not altered. The left kidney was like the right in all respects.

Bladder: The bladder was distended by a moderate amount of turbid yellowish urine. The mucosa which was slightly trabeculated was yellowish-white in color. The ureteral and urethral orifices were patent.

Prostate: The prostate was normal in size and shape and on section the parenchyma was seen to be firm, smooth and white. The testes were normal in size, shape and consistency. On section the light grayish-brown tubules strung out with ease.

Gastrointestinal Tract: The esophageal wall contained many longitudinal wrinklings. The mucosal surface was white in color. The stomach contained a small amount of dark gray mucoid material. Many rugae were present. The mucosa was dark red in color and a few petechial hemorrhages were seen. The small intestinal mucosa was also dark red in color but no other changes were seen. The ascending, transverse and descending colon were unaltered. There were a few scattered small diverticula of the sigmoid colon. These diverticula contained fecal material and were continuous with the lumen of the colon. The rectum was normal in appearance.

Bone Marrow: The deep red vertebral bone marrow was normal in appearance.

Organs of the Neck and Brain: Not examined.

Microscopic Report: Heart: Right Ventricle: The muscle fibers were enlarged as were their bizarre nuclei. There was a moderate amount of perivascular fibrosis present. The epicardium showed no changes.

Left Ventricle: The endocardial surface was covered by a thrombus which was undergoing early organization. The normal architecture of the irregularly thickened endocardium was disrupted by areas of hemorrhage, necrosis and accumulations of lymphocytes and polymorphonuclear leukocytes. Numerous dilated and congested capillaries and fibroblasts were seen in the deeper layers of the endocardium. Lymphocytes, polymorphonuclear leukocytes and connective tissue were present between the muscle fibers and around the blood vessels in the myocardium. Beneath the myocardium the wall of the aneurysm could be seen. The superficial surface of the aneurysm was covered by a thrombus. The wall itself was composed of dense acellular fibrous tissue. Dilated and congested blood vessels surrounded by lymphocytes and polymorphonuclear leukocytes could be seen in the depth of the aneurysm wall.

Right Auricular Appendage: The endocardial surface of the appendage was covered by thrombus and by clot. The endocardium was slightly thickened by lymphocytic and polymorphonuclear leukocytic infiltration. Lymphocytes were also present around the blood vessels in the myocardium.

Aortic Valve: The aortic cusps and the intervening commissure showed no changes other than fusion.

Pulmonary Artery and Aneurysm: The intimal surface of the pulmonary artery was covered by thrombus. Necrotic polymorphonuclear leukocytes and lymphocytes were seen in the intima. The intima was further thickened by fibroblasts. All the adventitia and the greater portion of the media were replaced by a necrotic amorphous eosinophilic material in which the remnants of polymorphonuclear leukocytes could be seen.

Thoracic Aorta; The intima showed no changes. There were a few lymphocytes and plasma cells around the medial and adventitial blood vessels.

Lungs: The pleura was markedly thickened by fibrous tissue, congested blood vessels and by lymphocytic infiltration. The alveolar septa, many of which were broken, were thickened by dilated and congested capillaries, lymphocytic infiltration and connective tissue. The alveoli contained red blood cells, polymorphonuclear leukocytes, lymphocytes and mononuclear wandering cells. There were hemorrhages in the walls of the bronchioles and also lymphocytic infiltration.

Liver: The capsule showed no changes. The efferent veins and sinusoids were markedly dilated and were filled with red blood cells. The adjacent liver cords were narrower than normal and the liver cells contained a few vacuoles and a slight amount of yellowish-brown pigment. The Kupffer cells also contained this pigment. There was a slight increase in connective tissue and lymphocytes in the portal areas.

Spleen: The capsule was not altered. The malpighian corpuscles were normal in number and cellular content but were decreased in size. The sinusoids were dilated and their lining cells were prominent. There was an increase in the amount of fibrous tissue and the number of red blood cells in the pulp. The walls of the arteries and arterioles were slightly thickened.

Pancreas: There was a slight increase in the interlobular and intralobular fat. The cells of the islets, ducts and acini showed no changes.

Adrenal: The cortical and medullary cells were normal in appearance. The capsule was not altered.

Kidney: The capsule showed no changes. There was a slight increase in fibrous tissue in the glomerular tufts. An occasional polymorphonuclear leukocyte was seen in the glomerular capillaries. A granular eosinophilic material was present in some of the tubules and in the glomerular space. Lymphocytes were present around the blood vessels in the cortex. The arteries and arterioles showed no changes.

Prostate: The acini and ducts varied little in size and shape. The lining epithelial cells of the former were heaped up and formed papillary projections. The fibromuscular stroma showed no changes.

Stomach: The mucosa was infiltrated with lymphocytes, polymorphonuclear leukocytes and a few plasma cells. The submucosa, muscularis and serosa were not altered.

Anatomical Diagnosis: Syphilitic aortitis, partial stenosis of coronary ostia, syphilitic aneurysm of ascending aorta, compression of pulmonary artery by aneurysm with narrowing of the lumen. Compression of left auricle by aneurysm. Hypertrophy and dilatation of right ventricle. Mural thrombus of right auricular appendage. Chronic passive congestion of liver and spleen. Congestion of lungs. Ascites. Cyanosis, marked. Pulmonary arteritis with overlying thrombus. Left auriculitis with overlying thrombus. Fibrosis of pericardium. Pulmonary emphysema, bilateral. Fibrous pleural adhesions, right. Chronic gastritis. Diverticulosis of sigmoid colon.

Discussion

The patient presented the clinical picture of acute primary cor pulmonale as shown by the rapid onset of severe dyspnea, orthopnea and cyanosis, evidence of right heart failure with distended neck veins and hepatomegaly, accentuated P_2, marked increase in venous pressure and markedly prolonged lesser circulation time. Evidence of left heart failure was absent. All the usual efforts used in treating heart failure were of no avail.

The etiology of the syndrome was a source of much discussion during life. Some felt that syphilitic aortitis was present because of the history of syphilis, a dilated aorta on the roentgenogram and the diastolic murmur at the base transmitted along the left sternal border. However, this explained inadequately the

clinical course of acute cor pulmonale. Others believed, because of the diastolic murmur at the apex, the accentuated P_2 and the enlarged left auricle as seen by fluoroscopy, that the patient had rheumatic heart disease with disease of the mitral and aortic valves and perhaps a concomitant syphilitic aortitis. It was difficult to account for the clinical picture on this basis, also, inasmuch as no signs of pulmonary congestion were ever noted until just before death, and the symptoms of the right heart failure were so severe and acute in onset.

It is difficult to explain the murmurs by the postmortem findings. Apparently there was no insufficiency of the aortic valve. The diastolic blowing murmur at the base and along the left sternal border may have been due to a relative insufficiency of the pulmonary valve from pulmonary hypertension, producing a Graham-Steele murmur. One can only conjecture as to the anatomical basis of the presystolic murmur at the apex. However, the only pathological change in the left auricle was that due to the pressure upon it by the aneurysm.

Several articles have appeared in the literature concerning the production of cor pulmonale by obstruction of the pulmonary artery by syphilitic aortic aneurysms. Garvin and Siegel,[1] in 1939 reviewed the literature and reported three personally observed cases. They stated that the usual result is rupture of the aneurysm into the pulmonary artery, but that rarely the aneurysm does not rupture but causes a stenosis of the pulmonary artery. This results in a burden on the right side of the heart, resulting in hypertrophy and dilation of the right ventricle, the so-called cor pulmonale. In their review, the aneurysm was located in the ascending arch of the aorta involving either the sinuses of Valsalva or the region just above the commissures, and bulged anteriorly and to the left, encroaching upon the pulmonary artery.

No case of aortic aneurysm with encroachment upon both the pulmonary artery and left auricle could be found in the literature. In the Glasgow Medical Journal of 1897,[2] a report is mentioned of the presentation of a heart containing two aneurysms, both arising above the aortic valve. One aneurysm projected against the left auricle. The case was that of a 38 year old woman who complained of severe symptoms of heart disease of 13 weeks' duration. "There were signs of cardiac hypertrophy with V. S. and V. D. murmurs heard most distinctly at the lower sternum."

Conclusion

A case of aortic aneurysm with encroachment upon the pulmonary artery and left auricle resulting in cor pulmonale and signs of left auricular obstruction is presented with the postmortem examination.

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The authors wish to thank Dr. I. Ogden Woodruff (Director of the First Medical Division, Bellevue Hospital) for his criticisms and suggestions in the preparation of this paper.

CASE REPORT OF DISSECTING ANEURYSM OF THE AORTA WITH CARDIAC TAMPONADE*

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ALTHOUGH dissecting aneurysm of the aorta with cardiac tamponade is not so rare as to warrant reporting in itself, this case is reported to stress the evolution of certain electrocardiographic changes noted in seriatim which may be of considerable diagnostic value.

CASE REPORT

On the morning of September 29, 1942, a white male adult 50 years of age was admitted to the Station Hospital. He appeared critically ill and complained of agonizing pain in the mid chest, back of the neck, throat, teeth, and both arms to the fingertips.

The patient stated that while he was standing in the field the pain and a gasping type of respiration suddenly appeared simultaneously in the above mentioned areas.

His previous personal history revealed the usual childhood diseases, tonsillectomy, and herniotomy. Seven years prior to admission he suffered an injury to the neck in an automobile accident, at which time there was a questionable fracture of a cervical vertebra. He had been known to have had a mild to moderate elevation of blood pressure for several years.

The family history was non-contributory except that the mother died of cerebral hemorrhage.

Physical examination revealed a critically ill middle-aged male adult. He appeared to be well oriented and in a state of collapse. The face was flushed. The fingers and toes were cold and clammy. There was no cyanosis and no difference in temperature or pulse of the two upper and lower extremities. The respirations varied between 50 and 60 per minute and were shallow and labored. The heart rate was found to be slightly rapid, but the sounds were of normal intensity. The blood pressure was 150 mm. Hg systolic and 90 mm. diastolic in both arms. He was well nourished and developed. Height was 5 feet 9 inches.

Progress. Soon after admission patient was given morphine sulphate, ½ grain by subcutaneous injection. It was thought initially that the patient was suffering from an acute myocardial infarction, but because of the character of the pain the possibility of a dissecting aneurysm of the aorta was considered. About one hour after admission, the heart sounds became distant and a gradually increasing number of ectopic beats made their appearance. The gasping respiration subsided, the rate coming down from 40 to 50 per minute to 16 to 20 per minute. Oxygen was administered intermittently through a BLB type oxygen mask. Some two hours later an electrocardiogram was taken. At that time only pain across the mid-thorax persisted and the patient stated that the character of this pain differed from the original but he could not describe in what way it differed. That afternoon a test dose of quinidine sulphate was given to start this drug because of the numerous ectopic beats and as prophylaxis against a possible ventricular fibrillation. The blood pressure during the day varied between 150 mm. Hg systolic and 90 mm. diastolic and 140 mm. systolic and 90 mm. diastolic. The number of ectopic beats lessened and the intensity of the heart sounds became normal. The following day there was much improvement in the general condition and the only complaint was a slight precordial and neck pain. Only an occasional ectopic beat was noted. No pericardial friction rub was heard. The pa-

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tient was placed on quinidine and aminophylline, grains 3 each three times daily. The electrocardiogram was interpreted as showing myocardial infarction (anterior). Detailed description of the tracings will be given later.

On the second hospital day patient was given pantopon, ⅓ grain, at 11:00 p.m. and 5:30 the following morning because of increased pain in the neck and upper back. The pulse had varied between 90 and 100 during the night. The blood pressure that day averaged 140 mm. Hg systolic and 104 mm. diastolic. The heart rate and rhythm were normal except that the A_2 became accentuated. On the third day temperature was 101° F., pulse 108, regular and of good quality. Fine crepitant râles were heard over both bases. The heart showed no abnormal sounds. The following day the patient was entirely comfortable except for mild headache and the crepitant râles were heard occasionally over the left base. On the fourth day the patient was distinctly better; blood pressure remained about 140 mm. Hg systolic and 90 mm. diastolic. The lungs were clear and the heart appeared to be normal. On the fifth day a pericardial friction rub was heard, best over the mitral area. General condition was good. The friction rub disappeared on the following day and the blood pressure averaged 138 mm. Hg systolic and 88 mm. diastolic, with a pulse of 90. On the morning of the seventh day the patient suddenly became anxious and restless and a cold, clammy sweat covered his body. The pulse was faint and difficult to obtain, and the heart sounds were found to be distant but regular. There was a sudden reappearance of severe pain over the entire precordium and the patient rapidly went into shock. An hour later a definite pulsus alternans appeared. The blood pressure was not obtainable. The apex rate was 98 with frequent ectopic beats and an apical systolic murmur, and an audible precordial friction rub was heard. Moist râles appeared in both lung bases. The patient was given morphine sulphate, ¼ grain, and oxygen was administered again. Soon after he was given 50 per cent glucose and aminophylline, 3¾ grains intravenously. Within two or three hours occasional pulse beats could be obtained, the extremities became warm, and the color appeared normal in the extremities. Marked perspiration continued; blood pressure was 90 mm. Hg systolic and 60 mm. diastolic. Respirations were 50 per minute. Another electrocardiogram that was taken the same morning showed no evidence of block or ventricular fibrillation. During the day there was gradual improvement and that afternoon the blood pressure was 130 mm. Hg systolic and 80 mm. diastolic. During the night there was a sudden collapse of the blood pressure again with a rising respiratory rate. The heart sounds became irregular and the temperature gradually rose to 106.8° F. per rectum. At that time the blood pressure was 90 mm. Hg systolic and 60 mm. diastolic and about three hours later had risen to 120 mm. Hg systolic and 80 mm. diastolic. His condition remained the same until the following morning when the patient suddenly coughed, went into collapse rapidly, and died soon after.

Laboratory Data. Soon after admission the urine was found to be normal. The blood count revealed normal red blood count and hemoglobin 90 per cent. There was a slight leukocytosis with a polymorphonuclear increase to 84 per cent with no shift to the left. Blood non-protein nitrogen was 40 milligrams per 100 c.c. The sedimentation rate (Cutler tube) was 10 mm. in 60 minutes. On the fourth hospital day the sedimentation rate had risen to 42 mm. in 60 minutes. Several urine examinations throughout the course of illness revealed no abnormalities except for a trace to 1 plus albumin and 8 to 10 leukocytes per high power field. The blood non-protein nitrogen on the third hospital day was 43 milligrams per 100 c.c.

Electrocardiographic Studies. (See tracings below.) The first tracing (first column on the left), about two hours after admission, showed a rate of 80 with a normal sinus rhythm. PR interval 0.15. P-waves, 0.1. QRS complexes 0.07. Deep S_3. T_1 diphasic. T_2 diminished amplitude. T_4 inverted. Marked left axis deviation. Interpretation: It was thought that the T-wave changes in Leads I and IV suggested an early acute anterior myocardial infarction.

Electrocardiogram, fourth day of illness (middle column): Rate, 104. Sinus tachycardia. PR interval 0.14. P-waves, 0.08. Splintered QS_3 and elevated ST_1 and ST_2. T_1 diphasic to inverted. T_2 diphasic to inverted. T_3 diphasic. T_4 inverted. Interpretation: Changes diagnostic of anterior apical myocardial infarction or acute pericarditis.

Electrocardiogram eighth and last day of illness (last column on right): Rate 110. Sinus tachycardia. PR interval 0.16. P-waves, 0.11. ST_2 segment elevated. Deep Q_3. Low R_3. Interpretation: As compared with previous tracings, the upright T_1, T_2, and T_4 indicated a reversion toward normal.

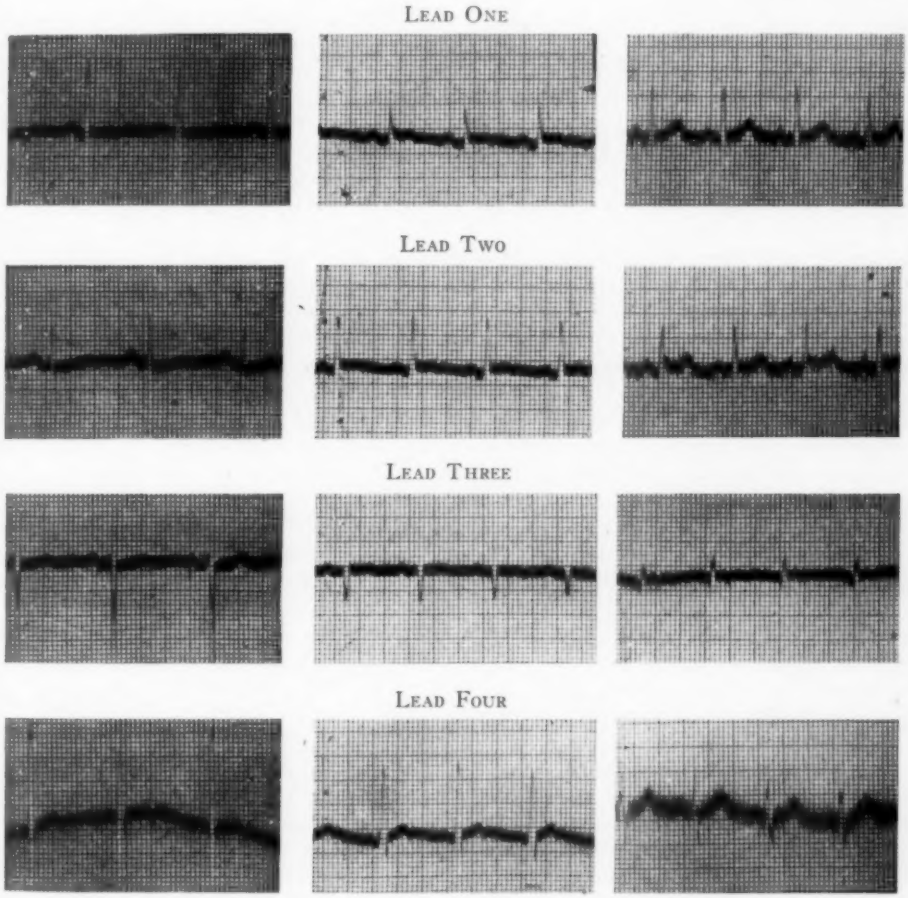

Fig. 1.

Autopsy Protocol

Pathological Diagnoses. 1. Hemorrhagic pericardial tamponade. 2. Dissecting aneurysm ascending portion (intrapericardial) of the aorta. 3. Serofibrinous and fibrinous pericarditis. 4. Aorta—arteriosclerosis. 5. Coronary artery—atherosclerosis. 6. Lungs—bilateral minimal pulmonary congestion. 7. Kidneys—benign nephrosclerosis (early). 8. Liver—focal degenerative hepatitis. 9. Brain—hyperemia (with diapedesis of red blood cells) of right parietal cortex.

Cardiovascular System. Gross findings of the cardiovascular system showed the pericardium to be quite distended. When it was opened, the parietal layer was found to be considerably thickened, measuring 0.3 cm. The pericardial sac was filled with free blood and cruor clot, representing a volume of approximately 500 c.c. A serofibrinous exudate covered the right auricle, right ventricle, and extended on to the anterior surface of the left ventricle. This exposure showed the right auricle to be slightly distended and the right ventricle definitely more distended. The ascending portion of the aorta was seen to be larger than normal and measured 10 by 4 cm. The aorta was dissected free at the aortic hilus and then opened, after removal, along the greater curvature up to the aortic valve. This dissection showed that at a point 12 cm. from the aortic sinuses there was a gradual thickening of the sheath about the adventitia up to a thickness of 2 cm. This circumscribed material covering that portion of the aorta was due to organizing extravasated blood. The examination of the intimal surface of the aorta showed a number of yellow atheromatous plaques, but no evidence of calcification in that region and no puckering and narrowing of the coronary orifices were noted. At a distance 3 cm. above the left posterior aortic sinus there was a transverse rent in the aorta approximately 1.5 cm. in length. The extravasated blood, confined within the sheath, extended far enough to cause possible compression externally upon the coronary orifices. The outer aspect of this dissecting aneurysm showed several circumscribed areas of organizing material, circular in arrangement, and up to 2 cm. across and 3 cm. in thickness. It was not possible to identify the point from which the blood had escaped through one of these areas into the pericardial sac. It is to be noted from the above that the entire dissecting aneurysm was intrapericardial. There was definitely no rupture of the heart itself.

After opening the right auricle, we found it to be intact. The right ventricle was ballooned out somewhat and was soft, red in color, and 0.7 cm. in thickness. The left auricle was also intact and contained no thrombi in the appendages. The chordae tendineae and papillary muscles were normal. The endocardium was normal. The myocardium of the left ventricle was deep red and firm, measuring 1.5 cm. at its greatest thickening. There was focal narrowing at the tip of the apex for a distance of 2 cm. where the depth of the ventricle narrowed to 1 cm. This area was composed partly of white fibrous connective tissue which was in sharp contrast to the surrounding red myocardium. The aortic valve measured 8 cm. across and was intact. Dissection of the right coronary and left coronary with its anterior ascending and circumflex branches showed the vessels to be patent throughout. In the first cm. of the right and first 4–5 cm. of the major branches of the left coronary there was evidence of atheromatous plaques but no calcification.

Respiratory System. Right lung, 410 gm.; left lung, 320 gm. Both lungs were somewhat similar in appearance, being grayish-black in color, with some reddening in both lower lobes. On cut section, they were pale gray, except in the lower lobes where there was deep reddening. No frothy or bloody fluid escaped. On opening the trachea and bronchi, particularly of the left side, there was abundant mucopurulent exudate which was quite tenacious but there was no evidence of dilatation of any of the bronchial passages. The peribronchial nodes were somewhat discrete and grayish-black in color.

Bacteriological Examination. Culture of pericardial fluid showed no growth.

Histopathology

Parietal Pericardium. The section showed the pericardium to be thickened by hyalinized connective tissue and serofibrinous exudate. In the latter there were some large cellular structures, ovoid in shape, with lightly vesicular nuclei. These structures resembled hypertrophied endothelial cells, perhaps acting as macrophages. Occasionally a mitotic figure was present in them. Diagnosis: Serofibrinous pericarditis.

Right Posterior Aortic Sinus. The intima and media were essentially intact, except for slight focal hyalinization, but again there was a thickening of the adventitia and surrounding sheath by granulation tissue and hemorrhagic exudate containing large numbers of polymorphonuclear leukocytes not seen in the previous section.

Arch of Aorta. The section showed the intima to be essentially intact. The media showed a longitudinal area where the muscle fibers had become necrotic. There were red blood cells in this rent. The adventitia was continuous with a surrounding mass of granulation tissue. In the latter there was no perivascular round cell infiltration—in fact, no alteration in the vessels themselves. Further sections showed a small amount of lymphocytic deposition about a vasum-vasorum in the peripheral portion of the media and adventitia. In some of these sections, in addition to the granulation tissue, the outer part of the sheath showed the presence of homogeneous pink-staining material and red blood cells, with very little suggestion of iron pigmentation. Bacteria stains were negative.

Another section of aorta taken through a grossly atheromatous plaque showed the subintima and media to be irregularly thickened by hyalinization, replacing muscle fibers, and by fatty changes, together with cholesterol deposition. The central degenerative changes in the media in this section were somewhat similar to those seen in the portion taken directly from the dissecting aneurysm, except that in this section the cholesterol clefts were so apparent. Diagnosis: Dissecting aneurysm and arteriosclerosis. An additional section showed a more recent extension of the process, with marked extravasation of sero-fibrinous material containing red blood cells and disintegrating leukocytes forming a very large mantle.

Descending Aorta. Diagnosis: Arteriosclerosis.

Apex, Left Ventricle. Diagnosis: Sero-fibrinous pericarditis.

Left Coronary. Diagnosis: Arteriosclerosis.

Bronchus, Left Lung. There was some hyperemia and hemorrhagic extravasation.

Left Upper Lobe. Hyperemia.

Right Lung, Lower Lobe. There was hyperemia of vessels and compression of many alveoli. Diagnosis: Early passive congestion.

Left Kidney. There was minimal thickening of the basement membrane of some of the glomeruli. The afferent arterioles appeared intact, whereas the interlobular arteries frequently showed subintimal hyalinization. Some of the proximal tubules contained pink-staining debris which was not from red blood cells. One of the branches of the renal artery showed early arteriosclerosis. Diagnosis: Early benign nephrosclerosis.

Liver. About the central veins there were present, in some instances, degenerating leukocytes but with some evidence of degeneration of hepatic cells in such areas. There was bile pigmentation. There was no fibrosis or proliferative activity. Occasionally, the leukocytic deposition was more extensive and more confined to the region of the central vein. Those areas of focal degeneration suggested early abscess formation. There was some scattered fatty infiltration. Diagnosis: Focal degenerative hepatitis.

Brain. Right parietal cortex showed hyperemia of the vascular channels with focal diapedesis of red blood cells. The latter often formed small mantles about those vascular channels with as then only very early necrosis of brain tissue. This focal lesion resembled the type so often seen in hypertensive individuals, as reported by Chase. The larger vessels in the sulci were essentially normal. Diagnosis: Hyperemia (with diapedesis of red blood cells).

The autopsy on this case was performed by Lt. Col. Stuart W. Lippincott who added the following note on the pathogenesis of the pericarditis and dissecting aneurysm: "At the time of autopsy, the size of the pericardium suggested the presence

of a tamponade, which was verified as soon as the pericardium was slit open. The thickness of the pericardium suggested that the pericarditis had existed for some time. On gross examination of the apex of the left ventricle, it was thought provisionally that an old, small myocardial infarct was present. However, this was not substantiated by microscopic section. Furthermore, the pericarditis was too diffuse to be accounted for by a small previous infarction. Cultures from the pericardial fluid were negative, helping to rule out a bacterial etiology. There was no indication that the pericarditis was associated with uremia. Examination and comparison of the pericardium and the intrapericardial dissecting aneurysm showed that in both there was evidence of recent hemorrhagic extravasation but that in addition there was old granulation tissue in both. It seemed, therefore, that the recent and old diffuse pericarditis was best explained as being associated with small recurrent extensions and leakage of the dissecting aneurysm, with organization until the final episode occurred, during which about 500 c.c. of blood escaped into the pericardial sac, death being due to the tamponade.

"The etiologic factor in the formation of the dissecting aneurysm was also of interest. In the region of the dissecting aneurysm there was very little evidence, grossly, of arteriosclerosis. For that reason other possible factors had to be considered. The age group that this man fitted into was considerably older than that usually associated with idiopathic medio-necrosis, but the man's aorta was small throughout for the size of his physique so that such an entity still remained as a possibility. Syphilis, disputed by most people as a possible factor in a dissecting aneurysm, was not present. Microscopically, periarteritis nodosa and a mycotic form of dissecting aneurysm were ruled out. Finally, microscopically, in the dissecting aneurysm, wide subintimal and medial evidence of arteriosclerosis was found and was directly associated with the formation of the lesion."

The evolution of the electrocardiographic changes worthy of note in this case were that on the first tracing soon after admission the patient showed T_1 and T_4 inversion with upward convexity of ST_4 suggesting an acute early anterior myocardial infarction. Three days later it will be noted that the further changes of T_1 and T_4, especially as compared with the first tracing, are diagnostic of anterior apical myocardial infarction. The last tracing, taken on the day prior to death when the signs and symptoms of severe cardiovascular collapse appeared, showed a reversion toward a normal tracing.

In studying this series of electrocardiographic films in relation to the autopsy findings, the following speculations seem reasonable. During the early phase of the patient's clinical course in which the chest pains were prominent, there was a bulging of the root of the aorta due to displacement by the subintimal hemorrhages so that narrowing of the coronary ostia could occur. When the last electrocardiograph was taken a few hours prior to death, presumably the further destructive processes of the dissection which eventuated in the out-pouring of blood into the pericardial sac caused a release of this contiguous pressure and again allowed an adequate patency of the previously compressed coronary artery. The drop in blood pressure probably played a part as well.

Although this is purely speculative, it seems to be a reasonable explanation of the changing electrocardiographic findings from that of coronary occlusion at the onset of the illness to what appeared to be an almost normal tracing only eight or nine days later.

Certainly if one should encounter an individual showing evidence of either dissecting aneurysm of the aorta or acute myocardial infarction clinically, such a series of electrocardiographic tracings would be of considerable diagnostic aid in the differentiation of the two entities.

SPLENIC NEUTROPENIA: REPORT OF A CASE WITH SPLENECTOMY *

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IN 1939 Wiseman and Doan [1] described a new syndrome closely related to congenital hemolytic icterus and essential thrombocytopenic purpura. The chief features of this condition are splenic enlargement accompanied by an absolute neutropenia in the peripheral blood. The neutropenia is relieved by splenectomy. These authors presented three cases in 1939 and five additional cases in 1942.[2] Moore and Bierbaum reported a similar case in 1939,[3] and Muether, Moore, Steward and Brown recorded another in 1941.[4] The purpose of this paper is to present one additional case also treated with splenectomy with favorable response.

CASE REPORT

The patient, T. H., is a 56-year-old white male pharmacist who was first seen in the plastic surgery clinic of the University Hospitals on October 1, 1942, because of a scar tissue contracture in the left popliteal space which prevented extension of the leg to more than 150 degrees. The patient had suffered from atrophic arthritis for about six years, and two years previously had fallen and sustained a deep laceration on the upper part of the calf which had healed very slowly leaving the scar. In the preliminary work-up, the white blood cell count was observed to be 1800 with 78 per cent lymphocytes and 22 per cent polymorphonuclear cells. Further questioning revealed that the patient had taken (estimated) 400 five grain tablets of sulfanilamide during the period of healing and from 100 to 150 grains of aspirin weekly, as well as unknown quantities of phenacetin. This medication was taken because of the moderately severe atrophic arthritis which involved the knees, back, shoulders, wrist, hands and neck. In 1938 while the leg ulceration was healing a white cell count was recorded as 2,400. His previous physician had placed him on yellow bone marrow of which he took about 100 capsules, because of the neutropenia. Later liver extract was given over a period of one year with no increase in white blood cell count.

He was advised to discontinue all medication and return for checks on the white blood cell count. On October 17 the red blood cell count was 5,200,000 with 18 grams of hemoglobin; the white blood cell count was 1,700 with 73 per cent lymphocytes, 14 per cent young neutrophiles, 4 per cent band forms; 2 per cent eosinophiles, 1 per cent basophiles and 10 per cent monocytes. On November 17 the white blood cell count was 1,400 and no neutrophiles were seen in the blood film. A sternal marrow biopsy which was taken at the same time revealed 29 per cent myelocytes, 12 per cent juvenile neutrophiles, 25 per cent mature neutrophiles, 4 per cent eosinophiles, 1 per cent basophiles, 26 per cent lymphocytes and 23 per cent nucleated red blood cells.

The presence of a normal bone marrow picture in the face of the marked neutropenia in the peripheral blood was confusing so the patient was admitted to the hospital on November 25 for more complete study. No complaints were present other than the disability from the leg contracture and arthritic deformities of the feet and wrists. The arthritis had been inactive for at least one year. The family history was negative for any type of blood dyscrasia. The past history was negative for chronic disease of any type except malaria during childhood which had been asymp-

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tomatic for at least 30 years. He had a tonsillectomy in 1937 with uneventful recovery. No record was made of the blood picture at that time.

Physical examination revealed a well developed, somewhat undernourished, white male who looked slightly older than the stated age. There was a faint tremor of the hands resembling that found in Parkinsonism and the facial expression was slightly mask-like. The skin was dry and scaly over the exposed areas. The eyegrounds were negative. The mouth was edentulous. The chest was clear throughout. The pulse rate was 80 with a regular rhythm. The blood pressure was 120 mm. Hg systolic and 80 mm. diastolic. There were no cardiac abnormalities. There was no tenderness in the abdomen. The spleen was palpable as a large, firm, movable mass, extending 6 cm. below the costal margin. The splenic notches were discernible. Over the left popliteal space was a scar measuring 12 by 4 cm. which held the joint so that extension was limited to 150 degrees.

The complete serial laboratory studies are given in the accompanying table. Because of the triad of arthritis, splenomegaly and leukopenia, the impression was gained that the patient was suffering from "Felty's syndrome." However, in the face of a

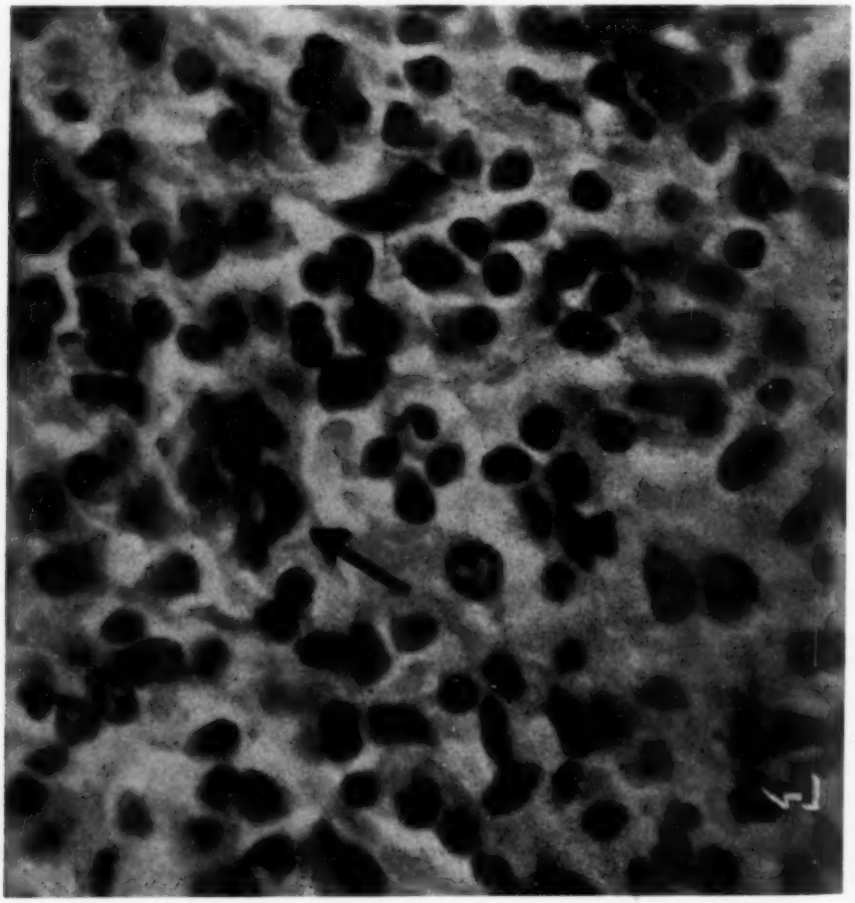

FIG. 1. Photomicrograph from paraffin section of spleen showing a phagocytic cell containing fragments of polymorphonuclear cells. Hematoxylin-eosin stain. Approximately × 1,000.

slightly increased icteric index, a mild degree of polycythemia, a normal platelet count and high normal reticulocyte count, it was suggested by one of us (W. L.) that this picture more closely resembled the primary splenomegalic neutropenia described by Wiseman and Doan.

On December 10 retrograde pyelography was done to demonstrate that the mass felt in the abdomen was not renal in origin. The left kidney was visualized as in the usual position and unrelated to the mass. On December 11, 1942, a splenectomy was done under general anesthesia by Dr. O. A. White. It was noted that the spleen was about four times the usual size with a thickened capsule and several small areas of white discoloration of the surface indicating a perisplenitis. There were no adhesions to the peritoneum or neighboring organs. The spleen weighed 720 grams. The gall-bladder contained one stone but was not removed.

Microscopic examination of the spleen revealed the capsule and septa to be fairly broad. Malpighian corpuscles were well developed and located at some distance from one another. There was some increase of the connective tissue stroma in the pulp. The capillaries in the pulp were filled with red blood cells and a number of granulocytes and their precursors. These were more numerous than normal in many areas. Definite phagocytosis of polymorphonuclear cells could be seen in the fixed tissue (figure 1). The pathological examination was done by Dr. Béla Halpert.

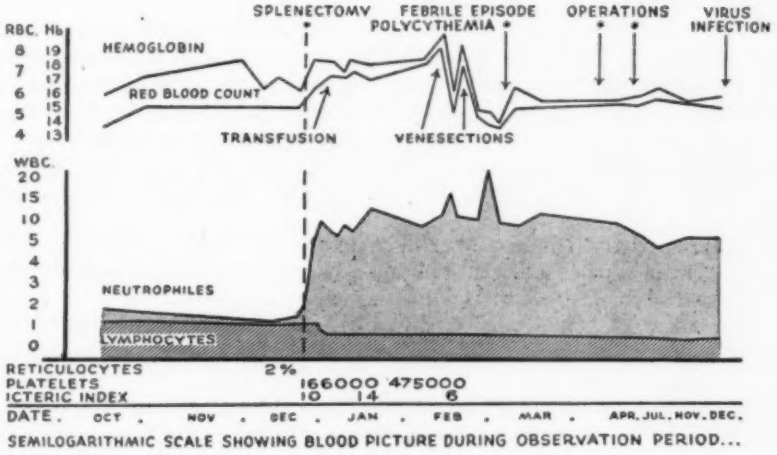

FIG. 2.

The postoperative course was uneventful except for a prompt rise in neutrophiles in the peripheral blood. The pre-operative white blood cell count was 2,800. In 12 hours the count had risen to 6,750 with 60 per cent neutrophiles. The preoperative platelet count was 166,050. Five hundred cubic centimeters of bank blood were given shortly after the operation. On December 14 the white blood cell count was 11,700 with 70 per cent neutrophiles. The blood picture is given in the accompanying table in serial form. On December 17 the icteric index was 14, though no clinical jaundice was visible.

The patient was discharged on January 5 with the wound completely healed. The white blood cell count was 14,600 with 63 per cent neutrophiles, 4 per cent eosinophiles, 1 per cent basophiles, 25 per cent lymphocytes, 7 per cent monocytes. The red blood cell count was 6,000,000, hemoglobin 17.6 grams. The platelets numbered 475,000.

Two weeks later on January 19, 1943, the patient returned to the Emergency Room

complaining of a severe headache and was obviously plethoric. He had had a chill 24 hours before and fever of 103° lasting two hours. The red blood cell count was 6,900,000 with 18 grams hemoglobin. A venesection was done and 500 c.c. blood were removed, which resulted in prompt relief of the headache. One week later the red blood count was 8,000,000 with 19.5 grams of hemoglobin. The headache had returned. The venesection was repeated and was again followed by relief. On January 31, 1943, he again suffered a severe chill with a fever of 104° and a pain in the left epigastrium. This series of chills with fever rise to 103 or 104° recurred daily and on February 2, 1943, he was re-admitted to the hospital. The pain later became localized in the left costovertebral angle.

The only physical finding of note was several small punctate hemorrhages of recent origin in the left retina. The red blood cell count was 5,500,000. Blood cultures and repeated examinations of the blood for malaria were negative. Nevertheless, 30 grains of quinine sulfate were given daily for 10 days because of the history of childhood malaria. Roentgen-ray examination revealed a thickened interlobar pleura on the left and obliteration of the left costophrenic angle. Cystoscopic examination with urinalysis of ureteral urine failed to reveal presence of infection. The daily white blood cell count during this febrile period ranged from 12,000 to 22,000.

By February 24, 1943, all symptoms had cleared up and though the etiology of the febrile disturbance was undetermined, it demonstrated that the usual neutrophile response to febrile infection was obtained.

On March 5, 1943, the scar tissue in the left popliteal space was excised and a split graft utilized to repair the defect. The leg was placed in full extension. On April 13, 1943, one small additional granulating area at the edge of the original graft was covered with pinch grafts. This healed uneventfully. On May 7, 1943, patient was discharged after intensive physical therapy designed to promote motion in the leg. The red blood cell count was 5,300,000 with 16 grams of hemoglobin. The white blood cell count was 9,400 with 68 per cent neutrophiles and 32 per cent lymphocytes.

The patient remained in good health and returned to his previous position as a pharmacist. In September and October, 1943, he was seen several times because of a contact dermatitis which proved to be due to laundry soap.

On November 14, 1943, a red blood cell count was 5,500,000 with 16 grams of hemoglobin. The white blood cell count was 7,250 with 75 per cent neutrophiles and 25 per cent lymphocytes.

He was readmitted on December 20, 1943, because of an acute tracheobronchitis, presumed to be of virus origin. This produced a fever of 100° on admission. The red blood cell count was 4,800,000 with 15.6 grams of hemoglobin. The white blood cell count was 8,600 with 55 per cent neutrophiles, 4 per cent eosinophiles, 1 per cent juveniles, 1 per cent basophiles, 34 per cent lymphocytes, 3 per cent monocytes. Spontaneous recovery occurred in four days.

The patient's arthritis improved symptomatically so that at the time of this report there were no symptoms other than residual deformities produced during the active phase. He was working full time.

Discussion

In 1933 Turley demonstrated that phagocytosis or perhaps extracellular enzymatic destruction of polymorphonuclear cells occurs in the spleen from a study of impression preparations of fresh splenic material, though the clinical significance of this was not recognized until some time later. He suggested that a hitherto unrecognized function of the spleen was disposal of polymorphonuclear cells in the normal individual. It was not until 1939 that the first published re-

ports of a clinical splenic neutropenia verified this function of the spleen. In this report, Wiseman and Doan postulated that the mechanism of production of the neutropenia was the excessive phagocytosis of neutrophiles by the clasmatocytes in the spleen. This process was considered an exaggeration of the phenomenon which occurs in the normal spleen. The removal of dead, effete or "senile" neutrophiles by the spleen is compared to the well recognized destruction of aging erythrocytes by the same organ. In several of their cases parallel phenomena of thrombocytopenia and hemolytic anemia were present, suggesting that the spleen itself had undergone a change in degree of activity so that not only the formed elements which had outlived their normal life span were destroyed, but also mature functional elements.

In the splenic neutropenia of severe degree practically all of the neutrophiles are destroyed. The presence of a normal or hyperfunctioning bone marrow is explained on the basis that it is not involved directly; instead the hematopoietic system is constantly attempting to regenerate cells in an effort to maintain the usual number in the peripheral blood stream.

"Felty's syndrome" of leukopenia, splenomegaly and atrophic arthritis resembles splenic neutropenia at least in the superficial features. This somewhat vague symptom complex has been questioned by Talkov et al.[5] as in many cases an atrophic arthritis is actually only a concomitant finding in various types of splenomegaly. It is of interest that two of Wiseman and Doan's cases and the present case had arthritic symptoms.

Splenic neutropenia is frequently precipitated by infection, or at least the clinical and hematological features become apparent during or following infections. One may equally suggest that the neutropenic individual is more susceptible to chance infection and that the infection merely calls attention to a hitherto unsuspected neutrophile deficiency.

The diagnostic criteria as laid down by Wiseman and Doan are:

A. Clinical—
   1. Splenomegaly
   2. Occasional purpura (thrombocytopenia)
   3. Occasional oral ulceration (neutropenia)
   4. Icterus, mild (hemolysis)

B. Hematological—
   1. Bone marrow
      a. Hyperplastic for myeloid series
      b. No abnormal cells
      c. Not leukemic
   2. Blood
      a. Marked specific neutropenia
      b. Anemia (macrocytic, hyperchromic)
      c. Reticulocytosis
      d. Increased serum bilirubin (depending on degree of anemia)
      e. Thrombocytopenia (variable)

(For a more comprehensive understanding, the reader is referred to their original description.[2])

Comment

This case has all the above features. Moreover this patient presented almost a "pure" splenic neutropenia, in which thrombocytopenia and anemia were practically absent, though a marked platelet rise as well as a transient polycythemia followed splenectomy. This suggests that some destruction of these elements was occurring but a compensatory hyperfunction of the myeloid tissue had managed to keep the platelet and erythrocyte count up to the physiologically normal level. The hyperfunction then continued for a period of about one month after splenectomy and subsided slowly.

The popliteal space infection corresponds well to the occasional oral ulcerations noted in other patients; in this individual careful oral hygiene and absence of natural teeth had probably prevented such complication. The postoperative infection, though not identified, resulted in a prompt neutrophile increase, demonstrating that the bone marrow was capable of a normal response to what may be presumed to be a pyogenic stimulus. A virus type of tracheobronchitis one year later did not result in leukocytosis.

A gradual improvement in the arthritis with disappearance of symptoms except for deformities produced during the acute stage further suggests that the arthritis may have been a sequel of the neutropenia. The rôle of this patient's childhood malaria in production of splenic overactivity is obscure.

Summary

A case of chronic splenic neutropenia is presented in a 56-year-old white male. Attention was called to the disease by routine blood studies preparatory to plastic surgery. The neutropenia was dramatically relieved by splenectomy. This was followed by a prompt rise in neutrophiles, platelets and erythrocytes in the peripheral blood. The syndrome was associated with atrophic arthritis.

Follow Up Report: Sep. 15, 1945. This man reports feeling exceptionally well, has missed no time from work, has no fatigue. Blood Count: Hb. 15.5 gm.; R.B.C. 5,880,000; W.B.C. 11,700; N. 59 per cent. Blood chemistry within normal range. Urinalysis negative.

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A SYNDROME TERMED REITER'S DISEASE (URETHRITIS, CONJUNCTIVITIS AND ARTHRITIS) *

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Although in the older German literature there were several cases suggestive of "Reiter's disease," it was not recognized as a clinical entity until 1916 when Reiter [1] described a clinical picture of urethritis, conjunctivitis, and arthritis which was non-gonorrheal in nature; therefore, credit must be given him for being the first one to recognize this "disease" and its symptomatology.

During World War I, Reiter observed the syndrome in a young officer who had become suddenly ill with abdominal pains and diarrhea which showed a slight admixture of blood. Two days after the onset a purulent urethral discharge developed, accompanied by a suppurative conjunctivitis and acute arthritis of the right knee. No gonococci could be demonstrated in the urethral and conjunctival discharges. The existing urethritis slowly improved without any local treatment, but three weeks after the onset there was an extension of the arthritis to the left ankle, right elbow and left wrist. The urethritis and conjunctivitis had disappeared by this time, but the patient suffered constantly from severe joint symptoms. The temperature varied for weeks between normal and 102.2° F., being higher in the evenings. Two months later there was an exacerbation of the conjunctivitis and this was soon followed by swelling of the prepuce and a marked cystitis. After the patient had been confined to bed for 10 weeks, his general condition showed gradual improvement. During the course of the patient's illness, Reiter was able to demonstrate a spirochete in the blood. Because of the peculiar boring movements of the organism in the dark field preparations, it was designated by him as "Spirochaeta forans." The organism differed from the pallida in that it was easily stained with methylene blue and diluted fuchsin solutions. The spirochete was non-pathogenic for guinea pigs, but mice perished in eight days with an enormous excretion of sweat. However, no spirochete could be demonstrated in the blood or organs of these animals.

On the basis of finding spirochetes in the blood of his patient, Reiter proposed the name of "Spirochaetosis arthritica" for this disease. Since that time no one has been able to demonstrate such an organism with the procedure set forth by Reiter. Until further investigation establishes a definite etiologic factor, it is better to call this a syndrome rather than a disease.

In succeeding years most of the cases reported have been in Germany. At the present writing there are approximately 65 cases reported in the literature, most of them originating in Europe. Pioneer work in the United States was done by Bauer and associates [2] at Massachusetts General Hospital, where in 1942 they reported six cases considered to be typical of this syndrome. Further studies are being done by these workers at the present time.[3]

The urologist is perhaps the first to encounter patients with this symptom-complex, because the initial symptoms are frequently related to the genitourinary tract. However, this condition is a problem not only for the urologist, but other clinicians as well. Reviewing some of our previous clinical records with other

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diagnoses, we believe that with our present knowledge of this disease, a few of them might have easily been classified as cases of the syndrome Reiter's disease. We are certain that there are many cases throughout the nation resembling this condition, but they have been inadequately or improperly diagnosed, either because of inadequate facilities or non-acquaintance with this syndrome. Most often these patients have been treated for a non-specific urethritis, acute conjunctivitis (including "pink eye") or "acute rheumatism."

Although we have only two clinical abstracts to present at this time, they illustrate the syndrome of Reiter's disease along with some of the more severe manifestations.

Case Reports

Case 1. Present Illness: A 30 year old white male was admitted to the hospital with the chief complaints of urethral discharge, mild joint pains, and smarting of the eyes. The following history was obtained.

At the age of 15 he was suddenly stricken with marked hematuria, a high fever and mild joint pains. In a few days a whitish to yellow urethral discharge appeared. At that time large blood clots were passed during urination with considerable pain in the urethra. A few days later a profuse purulent conjunctivitis developed with accompanying pain and photophobia. He was treated for cystitis, pyelitis and conjunctivitis. The symptoms subsided in about a month. Later a cystoscopy revealed a markedly injected bladder. All smears and cultures for organisms were apparently negative. The prostate was massaged bi-weekly for about one month because of slight enlargement. He had no further symptoms and changeable weather had no effect on his joints.

Four years later the patient again had symptoms of urethritis, cystitis, mild arthritic pains with slight swelling and conjunctivitis. He states that he had a fever of about 101° F. to 103° F. daily accompanied by pain across the lumbar areas and also an occasional chill lasting for only a few minutes. Dysuria and hematuria were present during the first few days of the attack. All laboratory tests were apparently negative again except for the blood and pus in the urine. The diagnosis of pyelitis with secondary cystitis and prostatitis was again made. The eye and joint symptoms subsided in a few days, and the patient was apparently well three weeks after the initial symptoms had appeared. No history of sexual exposure had been present. Shortly thereafter the patient was married, but marital relations had no effect upon his condition and there was no evidence of any pelvic or urinary disease in the wife. About six months later the patient again had similar symptoms for only a few days which quickly subsided with bed rest.

In August 1937, the patient stated that he was suddenly awakened by pain and swelling of the left elbow followed in 24 to 48 hours by extension to the right and left knee joints. The joints were "so painful that even a bed sheet could not be tolerated over them." This time the joints became markedly swollen with a massive effusion but there was only slight redness. In a few days a marked hematuria and urethral discharge of thick pus accompanied by a severe purulent conjunctivitis appeared. All smears for gonococci were negative. All cultures, blood serologic tests, agglutination, and complement-fixation reactions were negative. A non-hemolytic streptococcus was obtained from the blood but was later thought to be a contaminant when subsequent cultures failed. The patient remained in bed for two months and convalesced for another two months. During the course of his illness he had several mild chills with the temperature reaching 104° to 105° F. He was extremely toxic and even though the tentative diagnosis of pyelitis and cystitis with possible septicemia was made, the urologist was not satisfied with the diagnosis. Neo-

prontosil was administered but with no apparent effect. Absolute bed rest seemed to be the only helpful treatment. There were no residual joint symptoms. Prostatic massage was instituted after the acute phase of the illness had subsided. Later a cystoscopy revealed injection of the mucosa of the bladder but no disease of the kidneys was demonstrated. *E. coli* was cultured from the urine. No further symptoms were present and the urine had been normal on frequent examinations until the present illness.

Six months prior to this report the patient was seen as an out-patient when he began to have a slight whitish urethral discharge accompanied by burning and frequency. The urine 3 glass test showed cloudy sediment composed of many pus cells in the first two, but the urine sediment in the third glass revealed a few pus cells. The prostate was slightly boggy and tender, and the right seminal vesicle was apparently blocked. Prostatic smears after massage revealed many pus cells and diminished lecithin bodies. Sulfonamides had no effect on the course of the disease. It was felt at the time that most of the trouble was caused by the prostate, so biweekly massage plus diathermy daily to the perineum were started. Relief was obtained for a short time, but then the patient had mild arthritic pains and occasional urethral discharge. The conjunctivae were injected and a small amount of seropurulent material could be obtained. Smears failed to show any pathogens. He continued on duty until October 1944, at which time improvement was noted while on leave. After he returned to duty his symptoms recurred. On three occasions there was hematuria. Having lost 35 pounds of weight in six months, the patient was hospitalized for further study and treatment.

Personal and Family Histories: These were essentially negative.

Physical Findings: Normal findings were present except for the following: a moderate conjunctivitis and episcleritis of both eyes, profuse purulent urethral discharge, tenderness and swelling of the metacarpo-phalangeal joint of right index finger, mild tenderness but no swelling of both knees. Temperature 37.2° C., pulse 90, respirations 18.

Laboratory Data: Repeated smears of urethral discharge showed many pus cells with occasional gram-positive cocci. Prostatic smears (wet) revealed many pus cells and a few lecithin bodies but no bacteria. Smears of the conjunctival secretion revealed gram-positive cocci, some in short chains and others in clusters. Cultures of the eyes showed a few diphtheroid colonies and *Staphylococcus albus*, the latter being non-pathogenic on the basis of the coagulase test. The cultures of the urethral and prostatic secretions were negative except on two occasions when *E. coli* and *Staphylococcus albus* were grown. Repeated cultures of the urine failed to reveal any pathogens. All animal inoculations, including those for tuberculosis, failed to provide any new evidence. Blood films and cultures were negative. Scrapings of the urethra and conjunctivae were negative for inclusion bodies. Blood studies revealed: Red blood cell count 4,400,000 to 5,000,000 and white blood cell count 10,500 to 13,200 with a slight increase in the polymorphonuclear cells. Hemoglobin ranged from 85 per cent to 95 per cent. The sedimentation rates varied from a high of 18 mm. per hour to 12 mm. per hour and at the time of discharge from the hospital they had returned to normal. The uric acid and non-protein-nitrogen were within normal limits. Blood Eagle and Mazzini reactions, repeated complement-fixation tests for gonorrhea, and agglutination for typhoid, dysentery and Brucella groups were negative.

Repeated urinalyses showed: Specific gravity 1.008 to 1.022, acid reaction, trace to one plus albumin, occasional to frequent red blood cells, few to clumps of pus cells, no casts, and some mucous shreds and epithelial cells. Dark field examinations, Giemsa and methylene blue stains failed to show any spirochetes in the urethral discharges.

Additional Studies: Frei, Ducrey, and intradermal allergy tests were negative. The electrocardiogram was normal. Roentgenograms of the teeth, paranasal sinuses and chest were normal. No evidence of a focus of infection was found. Roentgenograms of the joints and long bones revealed no pathological change. All renal function tests, including intravenous pyelograms, were normal. Stool culture for pathogens was negative.

Course and Treatment: While in the hospital the patient was given a régime of complete bed rest, penicillin 20,000 Oxford units every 2 hours for 35 doses combined with sulfathiazole grams 1 every four hours and a nutritious diet. The symptoms subsided slowly and a prolonged convalescence of two months was prescribed after the patient was discharged. Apparently chemotherapy had very little if any effect on the course of the disease. Bed rest seemed to be the only positive therapeutic measure. Specimens have been sent to the National Institute of Health for further studies and virus determination. The results may not be known for several months.

Case 2. Present Illness: A 21 year old white male was admitted to the outpatient department complaining of pain in the back and a discharge from the penis of 24 hours' duration. A history of sexual contact during September 1944 on several occasions was obtained, the last exposure having been one day prior to admission.

The urethral discharge was mucopurulent in character and the pain was located in the left lumbar region and radiated around to the left abdomen but not into the testis or penis. The pain was intermittent in character and was unaccompanied by other symptoms. No history of hematuria or dysuria was obtained at that time.

Personal and Family Histories: The patient's last tropical service was in September 1943 in the West Indies but no history of any illness while serving in that region was obtained. The patient denied any previous venereal disease. At the age of six years he suffered from pneumonia and an appendectomy was performed during the same year. The family history was negative.

Physical Findings: Examination was essentially normal except for evidence of tenderness in the left lumbar area and a mucopurulent urethral discharge. The prostate was normal in consistency, shape and size.

Laboratory Data: Stained smears of the urethral discharge revealed occasional gram-positive cocci and a moderate number of pus cells. No gram-negative organisms were noted. Chocolate-agar cultures were negative for gonococci.

Treatment: This consisted of 125,000 Oxford units of penicillin, and owing to the patient's required presence in Texas, he was not given further treatment at that time.

Subsequent Course: The penicillin had no effect on his urethritis. The discharge became more profuse and the lumbar pain became more severe. He was admitted to another hospital on October 24, 1944. The diagnosis of pyelitis was made and the cultures of the urine and discharge failed to show any evidence of gonococci. Some cultures revealed gram-positive diplococci. Sulfathiazole was administered but because of the presence of a hematuria after one week of the drug, the sulfonamide was discontinued. However, the urethral discharge became more profuse. The patient was given 150,000 units of penicillin intramuscularly and the discharge subsided but the hematuria persisted. There was pus in all three glasses of urine. Cystoscopy was performed late in November 1944 at which time there was a marked hemorrhagic cystitis. The urine from both ureters was clear and free from pus. The patient developed an excoriation on the glans penis on November 8, 1944, which persisted after his discharge from the hospital in Texas. Dark field examinations and blood serologic reactions were negative for evidence of syphilis. The urethral discharge ceased on December 16, 1944.

While returning to New York the patient became ill aboard the train and was hospitalized at the U. S. Marine Hospital, Cleveland, Ohio, on December 23, 1944, complaining of severe pain in the back and reappearance of the urethritis.

Course During Last Admission: The physical and laboratory findings on admission were essentially those of previous studies. Repeated cultures failed to establish an etiologic agent. The patient had lost 22 pounds in weight in six weeks. The urine 3 glass test showed a small amount of pus in each glass on repeated examinations during December 1944 and January 1945. The discharge and back pain ceased January 16, 1945. Intravenous pyelography on admission revealed a dilated left kidney pelvis but in January 1945 a normal pyelogram was obtained. Repeated complement-fixation tests for gonococci and the dysentery groups were negative. Blood cultures failed to reveal any pathogens. Repeated inoculations in guinea pigs showed only *E. coli*. On February 2, 1945, there was marked cloudiness of the urine in all three glasses and pus cells were numerous on microscopic examination. A marked dysuria and urethral discharge developed February 3 and these were followed by a terminal hematuria beginning February 6. There was marked tenesmus at terminal urination with the passage of large blood clots, after which the patient was relieved. Morphine was required to give relief at frequent intervals.

The hematuria persisted and on February 14 a severe bilateral conjunctivitis developed. Four days later the patient complained of marked pain and swelling of both knee joints. On February 22 the hematuria and urethral discharge ceased, but the conjunctivitis and the arthritis remained. In three days there was swelling and mild redness of the right wrist joint. Salicylates had no effect on the course of the joint symptoms. All symptoms subsided gradually and there were no sequelae at the time of discharge on April 17, 1945.

Summary of Laboratory Data: The urine studies revealed a range from many pus and red cells during the illness to normal findings at the time of discharge from the hospital. Cultures of the urine showed occasional colonies of *E. coli* but no other bacteria.

Cultures of the blood, conjunctivae, urethra and joint fluids were all negative for pathogens. Guinea pig inoculations were negative except for recovery of *E. coli* in several of the animals.

Scrapings of the conjunctivae were sent to the National Institute of Health, Bethesda, Maryland. The report is as follows: "Diagnosis: chronic conjunctivitis, cause undetermined. The conjunctival scrapings are focally covered by a thin layer of stratified squamous epithelium. The corium consists of a loosely textured fibrous tissue irregularly infiltrated by lymphocytes, some larger mononuclear cells, and occasional polymorphonuclears. No possible etiological agents or inclusion bodies were identified."

The sedimentation rates remained high. They ranged from 25 mm. per hour to 20 mm. per hour.

Roentgenogram of the chest revealed normal findings. Roentgenograms of the bones failed to show any pathological process.

Blood counts performed at frequent intervals showed red blood cells 4.4 to 5 million; leukocytes 13,300 to 6,450; hemoglobin 80 to 95 per cent and normal differential counts. The blood picture was normal at time of discharge from the hospital. There was a wide variation in the prothrombin time. At the hematuria stage the prothrombin time was 31 per cent of normal, but improved gradually after cessation of the bleeding. At the time of dismissal it had returned to normal. Platelet counts, bleeding and clotting times and clot retractions were normal. Serum proteins were normal, as were the A G ratios.

Blood non-protein nitrogen and uric acid studies were normal. Repeated blood Eagle and Mazzini reactions were negative. All complement-fixation tests for gonor-

rhea were negative. Frei and Ducrey skin tests were negative. Dark field examinations, smears and cultures of the penile excoriations failed to reveal any pathogens. No definite etiological agent was discovered in this case.

Summary of Treatment. Many measures were tried. No response was noted after the administration of sulfonamides or penicillin. Vitamin K and calcium were given during the period of hematuria. Regardless of any therapy the patient continued to have symptoms. Bed rest is believed to be the only beneficial therapeutic measure in this case.

Incidence

There is no doubt in the minds of investigators that this syndrome occurs more frequently than reported in the literature. Almost all of the cases have been in young males, the majority having been in soldiers in the 20 to 30 year age groups. As far as we are able to determine there have been no cases reported in the negro race; however, when more work is done in this country there may be occurrences in this group also. The syndrome in an overwhelming majority is found in those without previous venereal history.

Symptoms and Clinical Features

The essential triad of symptoms has already been mentioned. However, there are other manifestations which should be cited. Lever and Crawford [4] reported cases of keratosis blennorrhagica without gonorrhea which were believed to be so-called Reiter's disease. Kuske [5] described nine cases of pseudogonorrheal dermatitis also having urethritis, conjunctivitis and arthritis. Kumer [6] discussed a rare feature of a pseudo-membranous and papulo-vesicular eruption not only involving the general skin, but also the mouth, nose, conjunctivae, prepuce and anus. Naegeli,[7] Wiedman,[8] and Kruspe [9] reported dermatological features in some of their cases.

Very rarely is there a septicemic course. A case was reviewed by Pfleger [10] which developed a peculiar type of septicemia accompanied by herpes of the cornea. Most of the cases develop a profuse purulent conjunctivitis and episcleritis with associated weeping and photophobia. Seldom does the temperature go above 38° C., but an occasional case has shown a fever of 39° to 40° C. Any complicating feature may give rise to a high febrile and marked toxic reaction. Night sweats are not uncommon.

Many have had their onset with a severe diarrhea, some even with a bloody flux; however, this symptom has not been constant enough to warrant its inclusion with the cardinal symptom-complex.

Excoriations and ulcerations of the penis have been present in a few cases. Most of the penile lesions occur as a result of the constant and profuse irritation from the urethral discharge. Pain in the perineum, suprapubic region, along the course of the urethra, and in the costovertebral regions may be present.

The joints are usually very painful; active motion is often impossible and passive motion produces excruciating pain. Polyarthritis is most frequently observed, but mono-articular involvement may occur.[11] There is often a marked synovial reaction which develops suddenly. One symptom may persist longer than others. Very few cases have suffered disabling features, however.

There are recurrences in about 20 per cent of the cases, with involvement of any or all of the three systems. The syndrome has a self-limited course—recovery usually being complete with little or no residuae.

The prostate is frequently involved and has a tendency toward abscess formation. The seminal vesicles may become engorged and blocked, but there has been no instance of epididymitis reported.

Etiology

The proof that Reiter's disease is an infectious process remains inconclusive, although evidence points to this probability. Very few investigators have recovered a definite bacteriologic agent. Reiter thought that a spirillum was responsible for this condition. Later studies showed that the causal agent is not a spirochete, since such an organism in succeeding cases has not been substantiated.

It has been observed by many workers that diarrhea often precedes or accompanies this syndrome. In the German armed forces an enteric polyarthritis frequently complicated by urethritis and conjunctivitis was extensively observed.[12] The factor of intestinal infection was considered. Many organisms have been cultured, most of them being non-pathogenic to animals. Gonococci have not been found in smears or cultures. The possibility that it is a venereal infection has been pretty definitely ruled out. No venereal history has been obtained in over 95 per cent of the cases and most cases have not had recent sexual exposure.

E. coli, pneumococci, *Staphylococcus albus,* "enterococci" of various types, diphtheroids, non-hemolytic streptococci, *B. xerosis* and *mucosus* are a few of the organisms found by investigators. Most of these organisms have not been recovered in animal studies. All cultures for tuberculosis have been negative.

Beigiböck [13] suggests the possibility of allergy as being the etiologic factor. There is no information in the literature that this question has been studied or evaluated. We were able to rule this out as a basis in our cases.

Most investigators report sterile cultures when using ordinary bacteriological media. Because of the course and refractory nature of this syndrome, we expect to search for a filterable virus in the future with the hope of finding an etiologic agent.

Laboratory Findings

In most cases the sedimentation rates are found to be increased; the rates rise and fall in relation to the acuteness of the attacks. Some may persist for a short time after the subsidence of the symptoms.

There is often a secondary hypochromic anemia, some cases revealing a red blood cell count near 3,500,000. The white cell count may be normal or elevated to 20,000. The average count hovers around 13,000 with the differential showing a slight increase in the polymorphonuclear elements.

The urine reveals many to clumps of pus cells, occasional to frequent red blood cells, traces of albumin, usually no casts, and normal concentration-dilution capacity.

The synovial fluids from the swollen joints fail to yield any causative agent. They show inflammatory cellular elements.

Serological tests for syphilis, complement-fixation for gonorrhea, and agglutinations for dysentery and Brucella have been negative. Non-protein nitrogen and uric acid studies are within normal limits. Thick and thin blood films have not revealed any foreign element or parasite in the blood stream.

Bauer and Engleman [14] give the best report on the pathological findings in the joints and synovial fluids. "The cytological and chemical alterations that occur in the synovial fluid are similar to the changes that have been observed in the specific arthritides. Biopsy of a joint during the acute phase reveals a markedly injected synovial membrane, which when examined microscopically shows intense hyperemia and small focal areas of acute inflammatory cellular infiltration, findings which are quite indistinct from the acute synovitis of either specific infection or rheumatoid arthritis."

Osteoporosis and atrophy of the bones may occur, especially in the subchondral areas. These are rare, however.

Diagnosis

A diagnosis of Reiter's syndrome is made by a process of elimination. The triad of urethritis, conjunctivitis and arthritis should make one suspect this particular entity after gonorrhea is ruled out by the negative history, smears, cultures, and complement-fixation tests. The presence of "sterile" cultures points to this symptom-complex. The course and the slow response to therapy make this condition more probable.

Because the arthritis may be the first and only symptom for a few days, it behooves us to differentiate this syndrome from the ordinary arthritides and rheumatic fever. Salicylates and chemotherapy apparently have no effect on Reiter's syndrome. The appearance of the urethritis and conjunctivitis will usually aid in differentiation.

Complications

Rarely do complications occur. Cystitis and prostatitis are the most frequent. Balanitis has been reported in several cases. Colby [15] reports changes in the upper urinary tract in three cases. One developed a prostatic abscess which drained through the urethra. This case also had a terminal hematuria. No joint disability occurred. Another developed hydronephrosis with right chronic pyelonephritis. Cystoscopy showed a diffusely reddened bladder. The third patient showed hematuria with renal dilatation, which was improved at the time of discharge. One of Sommer's [16] cases developed a marked cystitis.

Many urinary tract complications respond to the element of time. Our cases have not been free of their symptoms long enough to perform any instrumentation, but during the previous episode, a cystoscopy showed a hemorrhagic cystitis. A secondary pyelitis may also occur.

Eye complications are infrequent. Episcleritis, iritis, and keratitis have been observed. The keratitis failed to cause permanent scarring. Herpes of the conjunctivae and cornea have also been recorded. Rarely permanent bone and joint changes take place.

Treatment

Unfortunately, complete bed rest is the best treatment at our disposal at the present time. This has brought about slow but definite results. The average

case requires from six weeks' to three months' rest before the symptoms subside completely.

A nutritious diet and adequate vitamin intake are essential since the weight loss must be corrected and the appetite stimulated.

Beigiböck [17] used "arthigon" in many of his 10 cases with surprisingly good results. This is a vaccine which produces a foreign protein reaction. Some of the patients had been treated before with other means but without benefit. An accidental observation while treating a suspected case of gonorrheal arthritis which later proved to be one of "Reiter's disease," induced Beigiböck to use this vaccine in the other cases which now were definitely diagnosed as cases of Reiter's disease. Thus the preparation was used in all phases of the disease. The results were very encouraging. He concluded: (1) the attacks of arthritis ceased after several injections; (2) there was freedom from pain at least for a few days; (3) there was a diminution in the stubborn effusions; (4) the conjunctivitis disappeared quickly, not to appear again; and (5) there was a diminution in the urethral discharge. This vaccine appears to be used quite extensively for this disease in Germany. Other workers have used sterile milk or other foreign proteins with encouraging results. We contemplated using typhoid vaccine or the hypertherm on our first patient, but his condition improved to such an extent that fever therapy was not thought advisable.

Codeine and sometimes morphine may be necessary to relieve the excruciating pain in the joints. Heat to the involved joints gives some relief. Salicylates have no appreciable effect. Sulfonamides and penicillin do not alter the course of the disease. Some German workers have used various urinary antiseptics but no definite improvement was seen. Antispasmodics are often helpful in relieving the pain in the lower urinary tract. Sometimes rendering the urine alkaline lessens the dysuria. The use of boric acid packs to the eyes followed by a bland antiseptic ophthalmic ointment will alleviate some of the eye symptoms.

Watchful expectancy for complications and giving them immediate attention will often avert future and permanent disability.

Summary

We have endeavored to present two cases of the syndrome "Reiter's disease" in conjunction with a comprehensive review of the literature.

This syndrome is a definite clinical entity of unknown etiology, presumed to be infectious because of its clinical course. It is not due to gonorrhea and the possibility of its being a venereal disease is remote. The possibility that a virus is the etiologic factor is being investigated.

Complications are infrequent but may be very severe. The prognosis is usually good and recurrences are present in about one-fourth of the cases. There have been no cases cited in the literature which terminated fatally.

It must be assumed that the incidence is more frequent than appears from the literature. Since the syndrome is little known, many cases are not properly diagnosed or recognized.

In bringing the syndrome Reiter's disease to more general attention, especially to the clinician, bacteriologist, and pathologist, it is our hope that further study will be given to this disease. Then the etiology could be ascertained and the therapeutic measures improved and evaluated.

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EDITORIAL

MEDITERRANEAN ANEMIA

THIS interesting disease was first clearly recognized as a distinct entity by Cooley,[1] who described the condition as it occurs in a severe form in children. Although the disease is relatively uncommon, Cooley's observations have been confirmed and amplified by many subsequent observers.

The disease is characterized by an increasing anemia which usually is not notable at birth, but becomes evident during infancy or early childhood and which progresses without remissions and in spite of treatment to a fatal termination within a few years or even a few months. In somewhat milder cases it may not be recognized until the tenth or fifteenth year, and a few have survived into the twenties. There is progressive enlargement of the spleen and often of the liver, but no significant enlargement of the lymph nodes. The skin and sclerae are pale and yellowish, occasionally frankly jaundiced.

The blood shows a severe anemia which is microcytic and hypochromic in type, with usually a moderate reduction in the hemoglobin concentration. The red cell count is usually from 1,000,000 to 4,000,000 but is relatively higher than the hemoglobin or the volume of packed red cells. In blood films the red cells show highly characteristic changes. There is marked anisocytosis and poikilocytosis with a tendency to fragmentation of the cells and the development of bizarre distortions. The majority of the cells are small, although a few macrocytes are usually present, and they look thin and pale. There are usually (but not invariably) many "target cells," [2] with a narrow rim and a circular central area of dark stained cytoplasm, often connected with the rim by a narrow "bridge," but elsewhere separated from it by a colorless zone. Such cells, however, may occur in a number of other diseases, including sickle cell anemia.

In fresh wet films these abnormalities are even more conspicuous. Barrett [2] described bowl shaped cells with a thickened central area which he believed appear as "target cells" in stained films. There may be a tendency to ovalocytosis, but sickling has not been described.

Stained films show some diffusely polychromatophilic red cells, often many stippled cells, and usually many nucleated red cells which may be present in enormous numbers and justify the designation erythroblastic anemia. There are normoblasts and macroblasts but not typical megaloblasts. Reticulocytes are increased. There is often a leukocytosis, either lymphocytic or myeloid, which may be high and accompanied by many myelocytes and myeloblasts.

[1] COOLEY, T. B., and LEE, P.: Series of cases of splenomegaly in children with anemia and peculiar bone change, Trans. Am. Pediat. Soc., 1925, xxxvii, 29–30.

[2] BARRETT, A. M.: Special form of erythrocyte possessing increased resistance to hypotonic saline, Jr. Path. and Bact., 1938, xlvi, 603–618.

There is also an increased resistance of the red cells to hemolysis in hypotonic salt solution. Although the first trace of hemolysis may appear at about the same concentration as with normal control blood (0.46 to 0.44 per cent, but often much lower), most of the cells are undissolved in concentrations which hemolyze normal cells (0.4 to 0.3 per cent), and hemolysis may not be complete in 0.1 per cent salt solution, or even in distilled water. This resistance is due to the great thinness of the cells, which enables them to absorb a large volume of fluid before they reach a spherical shape and rupture. This is one of the cardinal features of the disease, although it may be observed, usually in less degree, in sickle cell anemia and other types of hypochromic anemia in which thin cells may be present.

There is usually some increase in serum bilirubin, and in the excretion of urobilin and urobilinogen, but evidences of hemolysis are usually mild. The fundamental abnormality appears to be a defect in blood formation, rather than accelerated destruction.

There is marked hyperplasia of the erythropoietic tissue, both extramedullary and in the bone marrow. This leads to peculiar characteristic changes particularly in the long bones and skull. The cortex is thinned and the medullary portion becomes widened and porous, so that in roentgenograms the trabeculae stand out like fine sharp spines, or "hair-on-end." The thickening of the bone may be so great that it gives the patient a mongoloid physiognomy, with high bulging forehead and prominent malar eminences. Similar changes, however, usually less marked, may occur also in severe cases of sickle cell anemia and familial hemolytic jaundice.

The cases reported have nearly all been in families of Italian and of eastern Mediterranean ancestry. Frequently two or more siblings are involved. In isolated instances, however, apparently authentic cases have been reported whose ancestry was Chinese, Negro, or Indian.

Interest in the disease was much increased by the observation of Wintrobe et al.[3] of a mild type of anemia in adults, which showed many of the cardinal features of Cooley's anemia of children. These observations have since been confirmed, notably by Dameshek[4, 5] and by Smith.[6] In most of these cases the anemia was slight and symptomless or virtually so. The red cell count was either moderately reduced or normal, occasionally somewhat increased. The cells, however, showed microcytosis and hypochromia, often in fairly marked degree. There were anisocytosis and poikilocytosis qualitatively similar to that in severe cases, which were usually well marked, and out of all proportion to the degree of anemia. Target cells

[3] WINTROBE, M. M., MATTHEWS, E., POLLACK, R., and DOBYNS, B. M.: A familial hemopoietic disorder in Italians, Jr. Am. Med. Assoc., 1940, cxiv, 1530–1538.

[4] DAMESHEK, W.: "Target cell" anemia: anerythroblastic type of Cooley's erythroblastic anemia, Am. Jr. Med. Sci., 1940, cc, 445–454.

[5] DAMESHEK, W.: Familial Mediterranean target-oval cell syndromes, Am. Jr. Med. Sci., 1943, ccv, 643–660.

[6] SMITH, C. H.: Familial blood studies in cases of Mediterranean (Cooley's) anemia, Am. Jr. Dis. Child., 1943, lxv, 681–701.

and oval cells were often present. The cells were thin, and they showed increased resistance to hemolysis in hypotonic salt solution. Films sometimes showed an occasional polychromatophilic or stippled red cell, but normoblasts were rarely found. Some splenomegaly, slight icterus and urobilinuria were occasionally present. In some cases an increase in nucleated red cells in the sternal marrow was demonstrated. Changes in the bones demonstrable in roentgenograms were usually trivial or absent.

The degree of the abnormalities noted in these cases varied greatly. In most of the cases they were moderate or slight. A few of the cases, however, showed gradations from this mild form to the severe type of Cooley.

One of the most interesting features of this group of mild cases is their familial occurrence, and their limitation to families of Italian and East Mediterranean origin. A study of apparently healthy members of the families of cases of outspoken Cooley's anemia has revealed that many of them show such minor abnormalities in the blood. In nearly all cases in which both parents could be adequately studied, abnormalities were found in both. The evidence is now convincing that these conditions are related, and that the disease depends upon an inherited constitutional defect.

The exact genetics involved in this inheritance has been a subject of study and speculation. Valentine and Neel[7] have recently reported an extensive study of four families, and have critically analyzed the published data bearing on the problem. The three theories which have been most seriously considered are: (1) The outspoken form of the disease is inherited as a recessive character, and the patient is homozygous for this factor, i.e., inherits the defect from both parents.[8, 5] (2) The disease (in either outspoken or mild form) is inherited as a dominant factor[9, 6] for which the patient is heterozygous; and the varying degree of its expression depends presumably upon modifying genetic or environmental influences. (3) It is inherited as two nonallelomorphic dominant factors, one from each parent.[10] A statistical study of the number of normal individuals, mild and severe cases in these families revealed data which do not correspond perfectly with any theory, but conform best to the first theory of a recessive type of inheritance. The heterozygotes, carriers of the defect, however, show sufficient abnormalities ("mild cases") to make possible their recognition as a rule. If this theory is true, this offers an unusual opportunity to study the distribution of a recessive factor.

Although the "carriers" do not develop severe anemia, they are in varying degree abnormal individuals. Valentine and Neel suggested for them

[7] Valentine, W. N., and Neel, J. V.: Hematologic and genetic study of the transmission of thalassemia (Cooley's anemia, Mediterranean anemia), Arch. Int. Med., 1944, lxxiv, 185–196.

[8] Moncrieff, A., and Whitby, L. E. H.: Cooley's anaemia, Lancet, 1941, ii, 648–649.

[9] Cooley, T. B.: Hereditary factors in the blood dyscrasias, Am. Jr. Child. Dis., 1941, lxii, 1–8.

[10] McIntosh, R., and Wood, C. L.: An inquiry into the genetic factor in Cooley's anemia, Am. Jr. Dis. Child., 1942, lxiv, 192–193.

the term "thalassemia minor," as contrasted with the full-blown disease, "thalassemia major." They must be differentiated clinically from the iron deficiency anemias, lead poisoning, rheumatic fever, various forms of splenomegaly, as well as sickle cell anemia and various types of hepatic disease, in which target cells and increased resistance to hemolysis may be found.

REVIEWS

The Chemistry and Physiology of the Hormones. Editor, FOREST RAY MOULTON. Eighteen contributors. 243 pages; 19 × 26 cm. American Association for the Advancement of Science, Washington, D. C. 1944. Price, $3.50 to members; $4.00 to others.

The Chemistry and Physiology of the Hormones is welcome at a time when there have been rapid advances in the field of hormones. It is made up of 17 papers which were originally presented in 1943 by outstanding investigators at the American Association for the Advancement of Science Gibson Island Research Conference. The original papers were revised in the light of the opinions expressed in the general discussion following their delivery and work appearing before the time of their final publication was included. The resulting compilation is an authoritative reference volume which should prove useful to the clinician as well as to the research worker.

Four papers are devoted to various aspects of the chemistry and the physiology of the pituitary hormones. The isolation, chemistry, and physiological activity of the adrenal hormones and of insulin are presented in four papers. Salter has reviewed the status of the hormonal iodine level of the blood in relation to thyroid function in a paper entitled "Euthyroidism and Thyroid Dysfunction." He points out the high degree of correlation between the clinical status of the patient and the hormone iodine levels of the blood but warns against the third use of the hormonal iodine level as an indicator of physiological status in all conditions.

The rapid advances made recently in the study of the adrenal and sex hormones have stimulated interest in some of their end products of metabolism. Two papers, "The Excretion of Steroid Hormones in Urine" and "Clinical Significance of Sex Hormones and 17–Ketosteroids," offer some interesting observations on the excretion of 17–ketosteroids by normal individuals and patients with various endocrinopathies. The qualitative and quantitative changes in the ketosteroid excretion in the diagnosis and in the prognosis of various endocrine disturbances are outlined. A paper by Schwenk presents some of the outstanding contributions to the synthesis of various steroids, presenting possible steps which might take place in the body. One needs a thorough knowledge of organic synthesis to follow some of these reactions. The application of any of these to in vivo synthesis is problematical as little is yet known about the synthesis of these substances in the body.

This series of papers serves to correlate many of the important findings in the hormone field and should prove a welcome addition to a scientific library. Over 1200 references are included in the bibliography.

M. A. A.

BOOKS RECEIVED

Books received during August are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Pulmonary Edema and Inflammation. Harvard University Monograph in Medicine and Public Health—Number 7. By CECIL K. DRINKER, M.D., D.Sc. 106 pages; 21.5 × 14.5 cm. 1945. Harvard University Press, Cambridge, Massachusetts. Price, $2.50.

Virus as Organism. Harvard University Monograph in Medicine and Public Health —Number 8. By FRANK MACFARLANE BURNET, M.D., F.R.S. 134 pages; 21.5 × 14.5 cm. 1945. Harvard University Press, Cambridge, Massachusetts. Price, $2.00.

A Primer of Electrocardiography. By GEORGE BURCH, M.D., F.A.C.P., and TRAVIS WINSOR, M.D. 215 pages; 24 ×15 cm. 1945. Lea and Febiger, Philadelphia. Price, $3.50.

Government in Public Health. By HARRY S. MUSTARD, B.S., M.D., LL.D. 219 pages; 21.5 × 14.5 cm. 1945. The Commonwealth Fund, New York City. Price, $1.50.

Clinical Parasitology. By CHARLES FRANKLIN CRAIG, M.D., M.A. (Hon.), F.A.C.S., F.A.C.P., Colonel, U. S. Army (Retired), D.S.M., and ERNEST CARROLL FAUST, M.A., Ph.D. 871 pages; 24 × 15.5 cm. 1945. Lea and Febiger, Philadelphia. Price, $10.00.

Fitografia Alergologica. By JOSE MARTORELLI. 195 pages; 23 × 16 cm. 1945. El Ateneo, Buenos Aires, Argentina.

COLLEGE NEWS NOTES

Life Membership

We are gratified to announce that Dr. Merton M. Minter, F.A.C.P., San Antonio, Tex., is a recent addition to the Life Membership roster of the College.

Many Fellows of the College who have been considering Life Membership would attain their ambitions and save money by completing their Life Memberships before the end of 1945. The Life Membership fee is deductible on Federal income tax returns. Reports are rife that there will be at least moderate reductions in the income tax rate in 1946. The maximum saving from a tax standpoint, therefore, may be made in completing Life Memberships in scientific organizations during the present year when the tax rate is at its highest level.

The Life Membership fee in the American College of Physicians is worked out on an actuarial basis, varying in amount from $100.00 for those 59 years of age or more to $300.00 for those 45 years of age or younger. Three hundred dollars is the maximum fee and from it $15.00 is deducted for each year of age over 45, up to the age of 59, after which time $100.00 is the minimum fee. Life Membership entitles each Fellow or Master to permanent privileges of membership, to the benefits of the Annual and Regional Sessions and to the official publications of the College, including Directories, Annals of Internal Medicine, etc. Each Life Member receives a framed certificate, and his name is inscribed on the Life Member Scroll at the College Headquarters. The College plan affords the member an opportunity of paying his full dues during his productive years and while his income is greatest, thus avoiding the burden of dues later in life. Quite aside from any personal advantages which Life Membership confers, members who can afford to do so should subscribe for the express purpose of putting the College in position, financially, to broaden its activities along lines which are clearly suggested at this time.

Enlistments and Retirements, A.C.P. Members

The College has previously reported the names of 1,923 of its members who have been on active military service, and herewith reports the names of 4 additional members not previously included, bringing the total to 1,927:

John E. Gordon, Boston, Mass. (Colonel, MC, AUS)
Seymour J. Gray (Associate), Chicago, Ill. (Lieutenant, MC, USNR)
Hugh R. Leavell, F.A.C.P., Louisville, Ky. (Lieutenant Colonel, USPHS, R)
Walter C. Nalty, F.A.C.P., Fort Bayard, N. M. (Lieutenant Colonel, MC, AUS)

The following members of the College have been honorably discharged:

Ernest L. Boylan, Portland, Ore. (Major, MC, AUS)
Margil Clinton Carlisle, Waco, Tex. (Captain, MC, AUS)
Lee Pettit Gay, St. Louis, Mo. (Major, MC, AUS)
Edward A. Hagmann, Billings, Mont. (Major, MC, AUS)
Andrew D. Hart, Jr., Charlottesville, Va. (Lieutenant Colonel, MC, AUS)
Herman Albert Lawson, Providence, R. I. (Lieutenant Colonel, MC, AUS)
F. A. L. Mathewson, Winnipeg, Can. (Group Captain, RCAF)
Milton John Matzner, Brooklyn, N. Y. (Commander, MC, USNR)
Edgar M. McPeak, San Antonio, Tex. (Major, MC, AUS)
Clark P. Pritchett, Columbus, Ohio (Major, MC, AUS)

Edward G. Thorp, Melrose, Mass. (Lieutenant Colonel, MC, AUS)
Frank Walker Young, San Antonio, Tex. (Colonel, MC, USA)

Gifts to the College Library

The following gifts of publications are gratefully acknowledged:

Reprints

Robert M. Craig (Associate), Chicago, Ill.—1 reprint
Theodore R. Failmezger, F.A.C.P., Lt. Col., (MC), AUS—1 reprint
Hyman I. Goldstein (Associate), Camden, N. J.—1 reprint
Robert E. Hobbs, F.A.C.P., Major, (MC), AUS—1 reprint
Mack Lipkin, F.A.C.P., New York, N. Y.—3 reprints
Edward W. Miskall, F.A.C.P., East Liverpool, Ohio—1 reprint
Carlisle Morse, F.A.C.P., Louisville, Ky.—1 reprint
Bernard M. Scholder, F.A.C.P., Lieutenant Commander, (MC), USNR—1 reprint
George X. Schwemlein (Associate), USPHS (R), Chicago, Ill.—1 reprint
James S. Sweeney, F.A.C.P., Colonel, (MC), AUS—1 reprint
William G. Talmage (Associate), Staunton, Va.—1 reprint
Alexander S. Wiener, F.A.C.P., Brooklyn, N. Y.—12 reprints

Also acknowledged through non-member sources are the following:
"The Role of Nutrition in Preventive Medicine," Mr. A. L. Rose, Vice President, Mead Johnson & Company
A radio address, "Adequate Medical Care," American network, "The Doctors Talk It Over," by Dr. David P. Barr, F.A.C.P., New York, presented to the Library on behalf of the Lederle Laboratories, one of the sponsors.

Report from the Office of the Surgeon General, U. S. Army

Pacific Medical Conference

One of the most important medical meetings of this war was held in the Office of The Surgeon General of the Army, Washington, July 30–August 1, and was attended by outstanding experts in surgery, medicine and disease control from all theaters of operation throughout the world.

Major General Norman T. Kirk, The Surgeon General, called the meeting "to pool the knowledge and experience of the men from the fighting fronts in order that the lessons learned thus far in the war can be more thoroughly applied than ever before in the conservation of human life."

In addition to about forty of the country's leading medical experts from the overseas theaters, General Kirk had officers from virtually every division and branch of the Office of The Surgeon General attend the meetings and thoroughly discuss all phases of medical and surgical care, supply, transportation, training, and related subjects.

Such problems as the redeployment of millions of men to the Pacific areas were discussed. It was pointed out that the transfer of such vast numbers of American troops will invariably present health problems, but does not make the job impossible or unnecessarily difficult because of the experience of three and one-half years of facing and successfully fighting and controlling disease hazards of these areas.

More effective means for the treatment and care of both wounded and sick

troops near the front was another principal question studied at the meeting. It has been proved in the campaigns to date that such care has paid great dividends in the saving of lives and the alleviation of suffering, and the methods used are to be extended as far forward and as rapidly as is humanly possible.

Prevention and treatment of tropical disease were among the major problems studied and discussed at the meeting. Medical Corps specialists declared, however, that because many of these diseases are unknown in the United States, a dread of them has been created out of all proportion to their actual harmfulness.

The problem of returning medical personnel who have served several years in Pacific areas to the United States and replacing them with personnel from this country and the European and Mediterranean Theaters was given special study.

Major General George C. Dunham Cited for Inter-American Work

Major General George C. Dunham, F.A.C.P., United States Army, once referred to as the "World's Greatest Bug Hunter" in a citation by the American Hospital Association, was decorated with the Distinguished Service Medal at a ceremony in the Office of The Surgeon General on August 9, 1945.

Major General Norman T. Kirk, The Surgeon General of the Army, awarded the Medal to General Dunham on behalf of the War Department, and Nelson A. Rockefeller, Assistant Secretary of State and former Coördinator of Inter-American Affairs, read the citation in the presence of a large group of Army officials.

The citation stated in part that "for performing exceptionally meritorious service in a position of great responsibility from January 31, 1942, to June 8, 1945, in his capacity as Director of the Division of Health and Sanitation, Institute of Inter-American Affairs, Office of the Coördinator, and later as President of the Institute, General Dunham made a great contribution to inter-American relations."

General Dunham, detailed by the Army to the Office of Inter-American Affairs is well known as the "flying doctor of the Americas," since he directs more than 1,000 health centers, anti-malaria and other disease control projects, food supply, medical and nutritional surveys and experimental stations in conjunction with health authorities of the Republics concerned. These activities are carried on from Chile to the Central American Republics. They can be found deep in the Amazon regions of Brazil, Bolivia and Peru, and extend from the Caribbean Republics to the Atlantic.

About 12,000 persons are under the command of General Dunham at the many and varied activities scattered over the Americas and include doctors, nurses, dentists, sanitary engineers and other personnel. This work is carried on in four languages and many dialects. Many of his colleagues in the Republics refer to him as the doctor to 25,000,000 patients.

Madigan General Hospital Dedicated

Dedication services were held at Madigan General Hospital, Tacoma, Washington, on August 20, 1945. On May 18, 1944, The Surgeon General reported that this installation, which was formerly Fort Lewis Hospital, be converted to a General Hospital for the Medical Department. This request was approved by the General Staff on May 26, 1944, and by the Federal Board of Hospitalization July 3, 1944. President Roosevelt signed the final papers on July 17, 1944.

Madigan General Hospital is named for Colonel Patrick S. Madigan, (MC), F.A.C.P. Colonel Madigan, after serving in France in World War I, remained in the Army, serving primarily as a neuropsychiatrist in this country and in the Philippines and Panama. At the time of his death, May 8, 1944, Colonel Madigan was stationed at Fort Belvoir, Virginia.

Brigadier General Charles C. Hillman, F.A.C.P., Awarded Legion of Merit

Brigadier General Charles C. Hillman, (MC), U. S. Army, has been awarded the Legion of Merit for service from August 1939 to August 1944. "As Chief of the Professional Service, Office of The Surgeon General, by his untiring effort and devotion to duty he was responsible for the development of this Service from a small pre-war division to a large, well balanced organization. Under his direction, physical standards were set up for the wartime Army, and professional direction was given to the blood plasma program and many other technical procedures which have been highly successful in the war effort."

Yugoslav Award to General Leon Fox and Staff

The Yugoslav "Medal for Services to the People" has been awarded to Brigadier General Leon Fox, F.A.C.P., Field Director of the United States Typhus Commission, and to three other members of his staff.

General Fox, a native of Birmingham, Alabama, was awarded the Order First Class, while the Order Second Class was given to Lt. Col. Edward Murray, Cedar Rapids, Iowa; Lt. Col. Charles Wheeler, Doon, Iowa, and to Naval Lt. Stafford Wheeler, a graduate of Harvard Medical School, who was killed in Bosnia, April 13.

Evidence of the Typhus Commission's services is shown by the fact that more than 2,000,000 persons have been immunized since the Commission came to liberated parts of Yugoslavia last January.

Promotions in the Army Medical Corps

From Lieutenant Colonel to Colonel:

Ralph Garnett Ball, F.A.C.P., Manhattan, Kan.

From Major to Lieutenant Colonel:

Laurence Coleman Milstead, F.A.C.P., Allentown, Pa.

Hubert McKibban Parker, F.A.C.P., Kansas City, Mo.

William Ward Rucks, Jr., F.A.C.P., Oklahoma City, Okla.

Surgeon General Announces New Officer Release Policy

Under date of September 14, 1945, Major General Norman T. Kirk, F.A.C.P., The Surgeon General, announced a revised point system which will return 13,000 physicians, 25,000 nurses, 3,500 dentists and an undetermined number of other Medical Department officers to civilian life by January 1, 1946.

Under the plan those Medical and Dental Corps officers who have 80 points, are 48 years of age or have been in the Army since before Pearl Harbor will be released as surplus officers unless they are specialists in eye, ear, nose and throat work; plastic surgery, orthopedic surgery, neuropsychiatry or are laboratory technicians. These specialists will be released if they were called to active duty prior to January 1, 1941.

This is a drastic lowering of points below the previous plan which was based on an adjusted service score of 100 for non-scarce Medical Corps officers and 120 for those in scarce categories.

A similar drastic reduction was made in the point score for nurses, who are now eligible for discharge if their rating is 35 or more, or if they are 35 years old. In addition, all married nurses and those with children under 14 years are eligible for immediate separation. Physical Therapists and Dietitians are eligible under the same conditions if their point score is 40 or more, or if they are 40 years old.

Veterinary Corps officers will be eligible for discharge if they have a point score of 80 or more, if they are 42 years old, or if they joined the Army prior to January 1, 1941.

Medical Administrative and Sanitary Corps officers with point scores of 70 or more, who are 42 years of age or have been in service since before Pearl Harbor will be released as surplus.

General Kirk added that in some cases essential officers may be retained by military necessity until replacements are shifted to their positions but none will be held in service after December 15, 1945, without their consent.

Every effort will be made to release these officers at the earliest possible moment consistent with military needs, General Kirk added.

It is also anticipated that, on the basis of an army of 2,500,000 men, a total of 30,000 doctors, 40,000 nurses and 10,000 dentists will be released by July 1946, and if the armies of occupation and troops in the United States are concentrated at large posts these figures will be exceeded. These figures represent approximately 70 per cent of the peak strengths at VE-Day of these corps.

Dr. Julian Ruffin Returns from ETO

Dr. Julian Ruffin, F.A.C.P., Civilian Consultant to The Surgeon General, has just returned from ETO, where he replaced Dr. Frederick Stare as clinician on Nutrition Survey Team No. 1. During the time Dr. Ruffin worked with this team, nutrition surveys were made in many cities in Germany.

Typhus Award Made To Dr. Francis G. Blake and Dr. Kenneth F. Maxcy

The United States of America Typhus Commission Medal was awarded by Major General Norman T. Kirk, The Surgeon General of the Army, Monday, September 10, to Dr. Francis G. Blake, F.A.C.P., Dean of Yale University School of Medicine, and to Dr. Kenneth F. Maxcy, Professor of Epidemiology at Johns Hopkins School of Hygiene and Public Health, for "exceptionally meritorious service." Dr. Blake's citation said in part: "Dr. Blake initiated and directed investigations of classical importance on the clinical features and prevention of scrub typhus. He made new contributions to the knowledge and control of a form of typhus fever of great military and civilian importance. His wisdom, energy and special competence assured the success of this mission and laid the basis for enduring benefits."

The Typhus Commission medal, which was authorized by the late President Roosevelt, is regarded as a high honor in this field of science. It has been awarded to date to only about 30 men.

Hospitals Named for Refresher Training Courses

The Office of The Surgeon General has recently announced that the following hospitals have been designated for professional refresher training of Medical Corps officers to extend over 12-week periods:

Cushing General Hospital, Framingham, Mass.
Mason General Hospital, Brentwood, Long Island, N. Y.
Valley Forge General Hospital, Phoenixville, Pa.
Kennedy General Hospital, Memphis, Tenn.
Newton D. Baker General Hospital, Martinsburg, W. Va.
Percy Jones General Hospital, Fort Custer, Mich.
Winter General Hospital, Topeka, Kan.
McCloskey General Hospital, Temple, Tex.
DeWitt General Hospital, Auburn, Calif.

Medical Corps officers desiring refresher training in neuropsychiatry will be permitted to serve the entire 12 weeks on the neuropsychiatric services and to rotate

through the various wards of the neuropsychiatric services in order to gain experience in all phases of neuropsychiatry.

Dr. William H. Sebrell Completes Overseas Survey

Dr. William H. Sebrell, F.A.C.P., U. S. Public Health Service, acting as Nutrition Consultant to The Surgeon General, has recently returned from a 3-months tour of duty in ETO where he acted as Nutrition Consultant to Major General Stayer. Dr. Sebrell directed the activities of the 5 nutrition survey teams operating in that area and proposed a permanent table of organization and equipment for such teams. At the request of General Stayer, he proposed an administrative organization for handling the data obtained, which proposal has in large part been accepted. Activities of the Medical Department and the food supply organizations were coördinated to the end that a more equitable food distribution in terms of need will result. Recommendations were made for improving transportation facilities for the distribution of food. This program, initiated in the Nutrition Division of The Surgeon General's office, is the first attempt yet made carefully to appraise the nutritional status of an entire nation and to control its food intake in terms of minimum physiological needs.

Enlistments of Doctors in Regular Army Sought

Major General Norman T. Kirk recently announced plans to interest Medical Corps officers who are serving for the duration of the war to apply for commissions in the Regular Army. Among the more important attractions which General Kirk listed are the following:

"1. The Regular Medical Corps officer will be assured a professional career offering broader possibilities in a larger field than the practice of the average civilian doctor affords.

"2. The training and the assignments of Army doctors will be arranged to aid the Army doctors in obtaining board certification for specialties from the recognized civilian specialty boards.

"3. Graduate training will be continued with the establishment of Army fellowships, residencies and special courses.

"In addition to the above attractions, which carry decided weight with any professional man, the Army affords security in its pension system, hospitalization care and other considerations not usually available in civilian practice."

The plans under this policy call for the establishment of graduate training programs at Army Installations where the residencies will meet the requirements of specialty boards and arrangements will be made for accrediting by the appropriate specialty boards. Another phase of the program includes the establishment of Army internships at selected Army general hospitals.

Plans outline a procedure for giving professional rehabilitation and specialized training to Regular Army Medical Corps officers who have been in administrative work during the war. These doctors who have not been able to engage in practice because of administrative responsibilities will serve as understudies with doctors who have been active in professional practice. This assignment will lead to continued professional service and eventually specialty board certification.

Medical Corps officers in the Regular Army will be kept in professional capacities without material interruption under this plan.

The advantages of a professional career in the Army will also be brought to the attention of medical students to interest them in an Army commission. Only those who stand scholastically in the upper third of their classes will be prevailed upon to consider the Army for a career.

Reserve or AUS officers now on active duty who desire consideration for commission in the Regular Army may forward through channels Statement of Interest to War Department Adjutant General's Office in accordance with the provisions of War Department Circular 243.

Civilian physicians and former Organized Reserve Corps and AUS officers now on inactive duty status may submit Statement of Interest direct to the Adjutant General's Office.

As of October 1, Dr. William B. Dublin (Associate), previously of Los Angeles, became pathologist at the Indianapolis City Hospital.

Dr. Andrew D. Hart, Jr., F.A.C.P., who has been serving as Lieutenant Colonel in the Medical Corps of the Army, has been retired and is back as professor of clinical medicine at the University of Virginia, Charlottesville.

In recognition of his work on the various types of Rh factors and their genetic transmission, the College of Physicians of Philadelphia awarded, on July 14, 1945, the Alvarenga prize for this year to Dr. Alexander S. Wiener, F.A.C.P., of Brooklyn. Dr. Wiener delivered the Alvarenga Lecture, "Rh Blood Factors in Clinical Medicine," before a combined meeting of the College of Physicians of Philadelphia and the Philadelphia County Medical Society on October 3.

The Alvarenga prize was established by the will of Pedro Francisco daCosta Alvarenga, of Lisbon, Portugal, an Associate Fellow of the College of Physicians of Philadelphia, "to be awarded annually on the anniversary of the death of the testator, July 14, 1883." The award is made for outstanding published work and it is customary for the recipient to deliver his treatise before the College.

Lt. Col. Theodore L. Badger, (MC), F.A.C.P., has recently returned from thirty-nine months of service overseas in the European Theater of Operations. He served there for two years as Chief of Medicine, Fifth General Hospital (Harvard Unit), subsequently being transferred as Consultant in Medicine and in Tuberculosis in England, France and Belgium. During the last six months he was assigned as Medical Consultant of the Normandy Base Section.

Col. Badger is now separated from active duty with the Army and will renew the practice of medicine and diseases of the lungs at 264 Beacon Street, Boston.

Dr. James L. McCartney, F.A.C.P., was released from active duty in the Navy on September 10, after forty months in uniform. He just returned from fourteen months in the Pacific, where he was Chief of the Neuropsychiatric Department of a Naval Base Hospital in the Marianas Islands. Commander McCartney was first commissioned in the U.S.N.R. in January, 1926. He is starting a clinic which will place special emphasis on the neuropsychiatric problems of returned officers and their families, and has opened offices in the Garden City Hotel, Garden City, Long Island, N. Y.

The Department of Medicine, Woman's Medical College of Pennsylvania, maintains an extensive library of films and slides, many of the films being 16 mm. Kodachrome silent films. Dr. William G. Leaman, Jr., F.A.C.P., Director of the Department, has kindly made these films and slides available to the College or to visiting speakers, who might desire to use them. Copies of the catalog and supplement of the films and slides can be obtained by writing or telephoning Miss Bruni, Department of Medicine, Woman's Medical College of Pennsylvania, Philadelphia 29, Pa.

Dr. Sarah I. Morris, F.A.C.P., who has been Professor of Preventive Medicine at the Woman's Medical College of Pennsylvania for several years, has resigned to accept an appointment as Resident Physician, and Professor of Hygiene at Wilson College, Chambersburg, Pa.

The Eighteenth Graduate Fortnight of the New York Academy of Medicine was held October 8–19, 1945. The subject this year was, "Contributions of the War Effort to Medicine." The program consisted of morning panel discussions; afternoon hospital clinics; evening addresses and scientific exhibits and demonstrations. Dr. Cornelius P. Rhoads, F.A.C.P., is the Acting President of the Academy. Col. William C. Menninger, (MC), F.A.C.P., delivered the Ludwig Kast Lecture on "Modern Concepts of War Neuroses." Dr. David P. Barr, President-Elect of the American College of Physicians and professor of medicine at Cornell University College of Medicine, gave a paper on "Physiological and Psychological Effects of Bed-rest," and Dr. George W. Thorn, F.A.C.P., of Harvard Medical School, was a guest speaker on "The Use of Human Serum Albumin in the Treatment of Edema of Renal and Hepatic Origin."

Every physician in the United States will receive during the coming months copies of a handsome new publication, "Your Doctor Speaks," issued by The Upjohn Company, leading manufacturers of pharmaceuticals. This book contains a series of health messages which have been appearing monthly in Hygeia, Parents Magazine, Life, Time, Newsweek and the Saturday Evening Post. The basic purpose of the book is to enhance the knowledge of the advances made by medical science and the doctor's ability to cope with disease, so that the public will seek medical attention whenever necessary and as soon as possible. The desire is to have the book placed in the physician's reception room where it will be available for patients to read.

The Fifteenth Annual Conference of the Oklahoma Clinical Society has been scheduled for November 26–29, 1945, at the Biltmore Hotel, Oklahoma City.

The Committee on Professional Education of the American Public Health Association announces it will undertake a program for the accreditation of schools of public health. The Association states the funds are made available through the generosity of the Commonwealth Fund and that Professor C.-E. A. Winslow, of New Haven, has been appointed counsellor in charge of the investigative work. Accreditation will be based on a visit to the institution by a representative of the Committee and other data. A copy of the report of the staff will be submitted to the administrative head of the institution before submission to the Committee on Professional Education, and the Committee will provide a hearing to him or his representative if desired. Decisions of the Committee will be finally subject to approval by the Executive Board of the Association. In certain cases, provisional accreditation may be granted, subject to the fulfillment of specified requirements within a stated time.

It is planned to concentrate first on the basic one year of training qualifying for the degree of Master of Public Health (in Canada, Diploma of Public Health). At the same time, or subsequently, a list of institutions will be accredited for the more advanced degree of Doctor of Public Health, perhaps involving specialization in particular administrative or clinical fields.

Dr. Stanton Tice Allison, F.A.C.P., has been recently appointed to the rank of Captain, (MC), of the U. S. Naval Reserve. Capt. Allison is Clinical Director and Chief of Medicine of the U. S. S. Benevolence, one of the Navy's newest hospital ships, on duty with the Pacific Fleet.

Dr. J. C. Geiger, F.A.C.P., Director of Public Health of the City and County of San Francisco, recently received notice of his nomination as Honorary Vice-President of the Egyptian Public Health Association, notification being submitted through Dr. A. M. Kamal, President of the Association.

Mr. Basil O'Connor, President of the National Foundation for Infantile Paralysis, announces that the 1945 March of Dimes amounted to $16,589,874, exceeding by more than fifty per cent 1944's unprecedented total.

The American Red Cross recently announced the appointment of Dr. Louis I. Dublin, assistant to the chairman of the American Red Cross and vice-president of the Metropolitan Life Insurance Company, to conduct a survey of child health in France, at the invitation of the French Government. Dr. Dublin is accompanied by Dr. Leona V. Baumgartner, well-known pediatrician on leave to the Red Cross from the New York City Department of Health, and by Mrs. Ida K. Fivian, bi-lingual secretary, instructor in foreign languages at Bradford Junior College, Bradford, Mass. The Red Cross representatives will collaborate in their studies with French health agencies and with American Red Cross civilian war relief workers already in France. The survey, which is expected to be completed within two months, will seek ways in which assistance from abroad can help French health agencies to meet the needs of children.

The memberships of the following physicians in the American College of Physicians have been terminated:

Associates

Max J. Fein, New York, N. Y.
Edward J. West, Providence, R. I.

Fellows

Merle Q. Howard, Wauwatosa, Wis.
William J. McNerney, Syracuse, N. Y.
William S. Rude, Ridge Top, Tenn.

"Socialized Medicine" is the title of an interesting publication in Vol. XXV, No. 2, of The Index, published quarterly by The New York Trust Company. It is interesting to note that industrial and financial institutions are frequently interesting themselves in so-called "socialized medicine" and it is gratifying that they are supporting the viewpoint of the medical profession at large.

Dr. J. D. Riley, F.A.C.P., State Sanatorium, Ark., has been elected President of the Arkansas Tuberculosis Association.

Dr. William Earl Clark, F.A.C.P., has been installed, as of July 1, 1945, as President of the Medical Society of the District of Columbia. Dr. Fred A. J. Geier, F.A.C.P., was elected first Vice-President, and Dr. William M. Ballinger, F.A.C.P., a member of the executive board.

Dr. Geier has been installed also as President of George Washington University Medical Society.

Dr. Hugh R. Leavell, F.A.C.P., Louisville, Ky., for many years Director of the City-County Health Department, has resigned to accept a public health post with the Rockefeller Institute of Medical Research. He is now serving as a Lieutenant Colonel with the UNRRA, in London.

Capt. Dar Delos Stofer, (MC), USNR, Kansas City, was recently awarded a commendation for meritorious and efficient performance of duty as executive officer of a fleet hospital in the South Pacific.

Dr. Coy C. Carpenter, F.A.C.P., Winston-Salem, Dr. Wilburt O. Davidson, F.A.C.P., Durham, Dr. Walter R. Berryhill, F.A.C.P., Chapel Hill, Dr. James W. Vernon, F.A.C.P., Morgantown, and Dr. Paul F. Whitaker, F.A.C.P., Kinston, have been appointed to the Advisory Commission of the new North Carolina Hospital Board of Control.

Dr. John W. Preston, F.A.C.P., Roanoke, Va., has been appointed to the Virginia State Board of Medical Examiners for a term of five years.

Dr. Christopher C. Shaw, F.A.C.P., formerly of Bellows Falls, Vt., was advanced from Commander to Captain in the U. S. Naval Reserve on August 2, 1945. Captain Shaw is Chief of Medicine at the U. S. Naval Hospital, Corpus Christi, Tex.

Lt. Col. Theodore R. Failmezger, (MC), AUS, F.A.C.P., was Chief of Medicine and later Commanding Officer of the 116th Station Hospital in New Guinea and later in the Philippines. During his period as Commanding Officer, his hospital was awarded the Meritorious Service Unit Plaque.

Dr. Thomas Addis, F.A.C.P., Professor of Medicine, Stanford University School of Medicine, San Francisco, was made a Fellow of the Royal College of Physicians of Edinburgh on July 17, 1945.

Dr. M. A. Shillington, F.A.C.P., Glendive, has been elected President-Elect of the Montana State Medical Association.

Dr. Nelson G. Russell, Sr., F.A.C.P., Buffalo, was recently honored at a special meeting of the city's advisory health board in recognition of his fiftieth anniversary of graduation from medical school.

Dr. Arthur Grollman, F.A.C.P., Professor of Experimental Medicine, Southwestern Medical College, Dallas, has been made Professor of Medicine and Chairman of the Department of Experimental Medicine.

Dr. Eugene P. Campbell, F.A.C.P., has accepted an appointment as Chief of Field Party, Division of Health and Sanitation, the Institute of Inter-American Affairs, and is located in Rio de Janeiro, Brazil.

Dr. Beatrice Berle, wife of Ambassador Berle, has inaugurated a series of lectures on various clinical and public health problems, in which three members of Dr.

Campbell's staff have already participated. On August 15, with Dr. Einor H. Christopherson, Colonel Harold B. Gotaas, Executive Vice President of the Institute of Inter-American Affairs, and a group of Brazilian public health physicians, Dr. Campbell participated in the dedication of seven health centers in the Amazon Valley. These health centers have been constructed and are being operated through the Inter-American Coöperative Public Health Program under the direction of Major General George C. Dunham, (MC), USA, F.A.C.P.

Kansas Medical Society Establishes Fund to Assist Returning Veterans

The Kansas Medical Society will raise a fund of one hundred thousand dollars to assist returning Medical Officers in obtaining postgraduate medical education. Dr. Harold H. Jones, F.A.C.P., Winfield, is Chairman. More than thirty-six thousand dollars is already available.

Dr. Hubert W. Smith, formerly Research Associate at the Medical and Law Schools, Harvard University, has accepted an appointment as Professor of Legal Medicine at the University of Illinois Graduate School. Dr. Smith graduated both in law and medicine, and has written many well known treatises on the subject of medicine and the law.

Dr. Harry J. Perlberg, F.A.C.P., Jersey City, has been elected President of the Radiological Society of New Jersey.

Correction

In the July issue of this Journal it was announced that Dr. Theodore Rothman (Associate), formerly of Paterson, N. J., had removed to Los Angeles where he had opened his office "for the practice of medicine." Dr. Rothman specializes in neurology and psychiatry, and not in internal medicine.

War-Time Graduate Medical Meetings

The sudden termination of active hostilities in both Europe and Japan, with the resultant anticipated redeployment and separation of physicians from service, has compelled the Central Committee to make preparations for the conclusion of the War-Time Graduate Medical Meetings. Unless more urgent demands are forthcoming, the activities will terminate as of December 31, 1945. The Regional Chairmen have already been communicated with.

Partial Schedule of Future Meetings

Region No. 4 (Eastern Pennsylvania, Delaware, New Jersey) Dr. B. P. Widmann, Chairman; Dr. J. S. Rodman, Dr. S. P. Reimann.

U. S. Naval Hospital, Philadelphia, Pennsylvania:

October 26—Recent Advance in the Treatment of Acute Intestinal Obstruction—Dr. E. L. Eliason or Dr. Robert Welty.

November 16—Clinical Significance of Diplopia—Dr. Walter I. Lillie.

REGION No. 23 (Nevada, Northern California)—Dr. S. R. Mettier, Chairman; Dr. E. H. Falconer, Dr. D. N. Richards.

Letterman General Hospital, San Francisco, California:

November 3—Uremia Following Urologic Surgery—Dr. Donald Smith.

Station Hospital, Camp Stoneman, Pittsburg, California:

October 20—Suppurations of the Chest—Dr. Clayton G. Lyon.

November 17—Plastic Surgery—Dr. George Pierce.

Hammond General Hospital, Modesto, California:

October 21—Diagnosis and Surgical Treatment of Brain Tumors—Dr. Edwin B. Boldrey.

November 21—The Use of Penicillin in Injuries and Infections—Dr. Horace J. McCorkle.

Station Hospital, Fort Ord, California:

October 27—Hemorrhagic States—Dr. Paul M. Aggeler.

November 17—Diseases of the Thyroid: Clinical Diagnosis and Management—Dr. Mayo H. Soley.

U. S. Naval Hospital, Mare Island, California:

October 26—Acute Sinusitis—Dr. Lewis F. Morrison.

November 16—Streptococcal Infections—Dr. Lowell Rantz.

ASF Regional Station Hospital, Oakland, California:

November 14—Diagnosis and Management of the Lymphomas—Dr. Ernest H. Falconer.

U. S. Naval Hospital, Treasure Island, California:

October 26—Peritoneal Injuries and Infections—Dr. Alson R. Kilgore.

November 16—Interpretation and Misinterpretation of Certain Laboratory Tests—Dr. James Hopper.

Station Hospital, Camp Roberts, California:

November 10—The Fundamentals of Endocrine Diagnosis—Dr. Roberto F. Escamilla.

REGION No. 24 (Southern California)—Lt. Comdr. G. C. Griffith, Chairman; Dr. W. A. Morrison, Capt. H. P. Schenck, Dr. J. F. Churchill, Maj. N. Nixon.

Birmingham General Hospital, Van Nuys, California:

October 24—Communicable Diseases—Major Norman Nixon.
Acute Infectious Mononucleosis—Captain Charles H. Marple.

November 14—Surgery of the Biliary Tract—Captain Howard K. Gray.

November 28—Thoracic Surgery—Captain W. L. Rogers.

ASF Regional Hospital, Camp Haan, California:

November 6—Hemolytic Streptococcal Diseases and Their Sequelae—Dr. Robert E. Solley.

AAF Regional Station Hospital, March Field, California:

October 16—Tumor Pathology—Dr. Edward Butt.
November 20—Compound Fractures—Commander P. E. McMasters.

Station Hospital, Camp Cooke, California (afternoon session) and Hoff General Hospital, Santa Barbara, California (evening session):

October 17—Traumatic Surgery of the Urinary Tract—Captain D. W. Atcheson.
November 7—Some Dynamics of Military Neuro-psychiatry—Major Alexander Blumstein.
November 21—Pericarditis—Lieutenant C. Sylvester McGinn.

Torney General Hospital, Palm Springs, California:

November 6—Psychosomatic Medicine—Major Milton Miller.
Headache—Captain Oscar Sugar.
November 20—Peptic Ulcer—Dr. William Boeck.

U. S. Naval Hospital, Santa Margarita Ranch, Oceanside, California:

October 25—Neurosurgery—Captain Everett Dickinson.
November 8—The Cancer Problem in the Service Personnel—Lieutenant J. S. Binkley.
November 22—Modern Concepts of Lepra—Dr. Maxmillian Obermayer.

U. S. Naval Hospital, Long Beach, California:

October 17—The Streptococcal Problem—Lieutenant Commander George R. Underwood.
November 21—Liver Disease—Captain John Ruddock.

U. S. Naval Hospital, Corona, California:

October 25—False Biological Reactions—Major Mark Beam.
Allergies—Major Iredell Hinnant.
November 8—Neuropsychiatry—Lieutenant Commander Nichols.
November 22—Tumor Pathology—Dr. Edward Butt.

Station Hospital, U. S. Naval Air Training Station, San Diego, California:

October 19—Psychosomatic Medicine—Major Milton Miller.
Headache—Captain Oscar Sugar.
November 2—Recent Developments in Diabetes—Dr. James Sherrill.
November 16—Problems in Urology—Lieutenant Commander Rusche.

AAF Regional and Convalescent Hospital, Santa Ana Army Air Base, California:

October 18—Endocrinology—Dr. Hans Lisser.
November 6—Tuberculosis Problems—Commanders W. L. Rogers and A. W. Hobby.
November 20—The Use of Products of Fibrinogen and Thrombin in Otolaryngology—Captain Harry P. Schenck.

U. S. Naval Hospital, San Diego, California:

November 1—Dysenteries—The Differentiation Between the Protozoal and Bacillary Dysenteries—Dr. John F. Kessel.

U. S. Regional Hospital, Pasadena, California:

November 12—Thyroid Disease—Lieutenant Commander George Crile.

Publication of Membership Roster Postponed

Early in the summer it was proposed to publish a revised Membership Roster of the American College of Physicians. To that end data were collected from members.

The end of the War in Europe and in the Pacific, with the subsequent shifting of Medical Officers and innumerable changes of addresses, makes it impractical to publish a complete Roster this year. Therefore, only a new and revised Supplement to the last Membership Roster (1943) will be published. This will be distributed to members in the late autumn.

It is hoped that the College can resume the publication of a complete Directory in 1946, for it is anticipated that the majority of its more than 1,900 members who are now on military service will have been retired to inactive status in the meantime.

OBITUARIES

DR. GEORGE H. MEEKER

Dr. George H. Meeker, former Dean of the Graduate School of Medicine of the University of Pennsylvania, died September 4, 1945, at the age of 74.

Dr. Meeker was born in Philipsburg, N. J. He graduated from Lafayette College in 1893 and from the Medico-Chirurgical College of Philadelphia as a doctor of pharmacy in 1906 and thereafter completed a course in dentistry at the same institution. He did clinical research at the University of Munich, Germany. He had received honorary degrees from Ursinus College, Lafayette College, Villanova College and the University of Pennsylvania.

Although not a physician, he was Dean of the Medico-Chirurgical College until its merger with the University of Pennsylvania in 1916; from 1924 to 1928, he was also Director of the Graduate Hospital, and his Deanship of the Graduate School of Medicine extended from 1917 until 1941, when he retired. He was a member of the Masons, the Union League, Delta Upsilon, Phi Rho Sigma and Psi Omega fraternities, the American Pharmaceutical Association and the American Chemical Society. In 1906 he was the recipient of the Franklin Institute Medal for his contributions to science. A Clinic in Cincinnati, Ohio, was named in his honor.

Dr. Meeker will be remembered by a great host of physicians who studied in the Graduate School of Medicine of the University of Pennsylvania, and who received advice and aid from him. Dr. Meeker's unvarying objective was to establish in Philadelphia the finest and best school for postgraduate education in America.

COLONEL CHARLES McCABE DOWNS

Colonel Charles McCabe Downs, of the regular Army Medical Corps, (Associate), has been reported killed in action on June 1, 1945. His candidacy for advancement to Fellowship would have been presented for action at the next meeting of the Credentials Committee and the Board of Regents.

Colonel Downs was born at Casey, Illinois, March 9, 1900. He held the degrees of B.S. and M.D. from Indiana University. He immediately entered the Medical Corps of the U. S. Army and interned at the Letterman General Hospital, San Francisco. His tour of duty preceding the war included the Letterman General Hospital in San Francisco and the Gorgas Hospital in Ancon, Panama, and his later assignments included: Commanding Officer, 2nd Medical Squadron, 2nd Cavalry Division, October 1, 1941–July 15, 1942; Surgeon, 9th Armored Division, July 15, 1942–October 6, 1943; Commanding Officer, 110th Evacuation Hospital, Semimobile, Camp Swift, Texas, October 6, 1943–December 18, 1943; Surgeon, X Corps, December 18, 1943–. From July 5, 1944, he was serving in the Southwest

Pacific area, and on October 20, 1944, he landed in the Philippines, where he lost his life on June 1, 1945.

Colonel Downs was a Fellow of the American Medical Association and a member of the Association of Military Surgeons of the United States. He had a splendid record in the Army, and was considered well qualified in Gastroenterology and Pediatrics particularly.

EMANUEL KLAUS

Born May 4, 1875 of Joseph M. and Hannah Klaus in Cleveland, "Manny," as he was affectionately known, attended Public School and matriculated in the School of Pharmacy, Western Reserve University. Graduated in 1892, at the age of 17, he practiced pharmacy for six years.

In 1898 he entered Western Reserve University Medical School and graduated in 1902. His immediate and lasting association was Lutheran Hospital on the West Side of Cleveland. He established his practice in its environs, eventually specializing in Internal Medicine. He was a pioneer in anesthesia.

While he was internist on the staff of Lutheran Hospital, he likewise held the office of Chief Anesthetist until 1937.

Owing to his interest in anesthesia he became associated with the late Dr. F. H. McMechan and served as vice chairman of the Board of Governors of the Society of International Anesthesia Research from 1925 to 1939, at which time he succeeded Dr. McMechan as Executive Secretary and held the post until his death.

Five years ago the Society awarded him a trophy "in appreciation of his devoted service to the world conquest of pain in behalf of a suffering humanity."

He was a member of The Temple and The Temple on the Heights. He rose to the 32nd degree of Masonry and was a member of the Shrine and Grotto.

He enjoyed the association of the A. M. A., American Board of Internal Medicine, Society of International Anesthesia Research and was a life member of the American College of Physicians.

Entering medicine in one war, the Spanish American, he served in the First World War as Captain in the Medical Corps at Camp Zachary Taylor, Kentucky and died during the Second World War on March 21, 1945. But he, peaceful, warm and kind, was the antithesis of war.

The world and particularly the West Side of Cleveland cannot help being better that "Manny" Klaus was born. It is a sad but true commentary on human nature that we are most conscious of the Good after it is gone. But the ideals which "Manny" begot in the minds of those who knew him are deathless forms. In living, "Manny" was a credit to man, to his Maker, to his race and to his art.

FRANK J. DORAN, M.D., F.A.C.P.,
Cleveland, Ohio

DR. ABRAHAM RUDY

Abraham Rudy, M.D., F.A.C.P., Boston, Mass., died February 19, 1945, of pulmonary neoplasm, aged 50. Dr. Rudy was born in Bialystok, Poland, February 20, 1895. He was naturalized in the United States of America in 1928. His training was received in his native land of Poland, at the Academie de Caen, Rouen, France, and XI Gymnasium, Moscow. He graduated in medicine in 1923, Friedrich Wilhelm's University of Berlin. In this country he did postgraduate work at the Psychiatric Institute, Morristown, N. J., New York Post-Graduate Medical School, and Harvard Medical School.

Dr. Rudy had been on the faculty of Tufts College Medical School since 1929. He was Associate Visiting Physician, Chief of the Diabetic Clinic, and Consultant in Diabetes, Beth Israel Hospital; Visiting Physician and Consultant in Diabetes, Jewish Memorial Hospital; and Consultant in Diabetes, Jewish Tuberculosis Sanatorium, Rutland. Dr. Rudy was a member of many medical organizations, and had been a Fellow of the American College of Physicians since 1942. He was the author of numerous published articles and of "Simplified Diabetic Manual" and "Practical Handbook for Diabetic Patients."

DR. FRANK NEAL

Frank Neal, M.B., M.R.C.S. (England), L.R.C.P. (London), F.R.C.P. (Canada), F.AC.P., Peterborough, Ontario, Canada, died suddenly of a heart attack on January 18, 1945. His death has not previously been recorded in these columns.

Dr. Neal was born at Brussels, Ontario, September 3, 1879. He received his degree of Bachelor of Medicine in 1903 from the University of Toronto Faculty of Medicine. He later did postgraduate work in London, England, and became a member of the Royal College of Surgeons of England and a licentiate of the Royal College of Physicians of London. For many years he was connected with the Nicholls Hospital and St. Joseph's General Hospital of Peterborough. He was Consultant in Internal Medicine at St. Joseph's General Hospital, Director of the Diagnostic Chest Clinic of the Peterborough Health Association, Director of the X-Ray Department, and Consultant in Chest Diseases at the Nicholls Hospital, and Director of the Standard Medical and Surgical Clinic.

Dr. Neal had been President of the Ontario Medical Association, 1933–34; a Counsellor of the Canadian Medical Association, 1933–35; Chairman of the Ontario Laennec Society, 1934–35; and Vice-President of the American Therapeutic Society, 1934–35. He had also been President of the Ontario Radiological Society, and was a member of the Radiological Society of North America. Dr. Neal became a Fellow of the American College of Physicians in 1923. Like many other medical men in these times,

he had been working much too hard for some years, and at the end of a particularly heavy day, while examining his last patient about 6:30 in the evening, he collapsed and died before help could reach him.

DR. DONALD RENWICK FERGUSON

The many friends and former students of Major Donald Renwick Ferguson of Philadelphia, Pennsylvania, were shocked to hear of his sudden death from a cerebral hemorrhage at Camp Shanks, New York, on Monday, August 27, 1945.

Major Ferguson was born at Ben Avon, Pa., November 21, 1889. After graduating from the Central High School in Philadelphia he attended Swarthmore College and received the degree of A.B. in 1912. He then pursued his medical studies at the Hahnemann Medical College and graduated in 1916. He served as Chief Resident at Hahnemann Hospital, 1916–1917, and served in the First World War as Captain in the Medical Corps from 1917 to 1919. On the termination of the First World War he returned to Philadelphia and became associated with the teaching corps of the Hahnemann Medical College of Philadelphia, serving as Associate Professor of Medicine and later as Clinical Professor of Medicine. In 1938 he was made visiting physician to the Hahnemann Hospital of Philadelphia. He also served as visiting physician and cardiologist at St. Luke's and Children's Hospital and consulting cardiologist at the Women's Homeopathic Hospital.

Major Ferguson took an active interest in various medical organizations and served as President of the Homeopathic Medical Society of the County of Philadelphia. He was also a member of the Board of Control of the American Institute of Homeopathy, Secretary of the Homeopathic Medical Society of the State of Pennsylvania and was a member of the Oxford Medical Club, Philadelphia County Medical Society, Medical Society of the State of Pennsylvania and the American Medical Association.

He became an Associate of the American College of Physicians in 1923 and a Fellow in 1928. At the break of the Second World War, Dr. Ferguson volunteered his services in the Medical Corps and served as a Major from September 25, 1942, until the time of his death.

Dr. Ferguson will always be remembered by those with whom he was associated as an exponent of the highest ethical standards in medical practice and as a forceful and enthusiastic teacher in his chosen field of clinical medicine. His loss will be deeply felt by his many friends and by the institutions that he served so faithfully and so long.

G. HARLAN WELLS, M.D., F.A.C.P.,
Philadelphia

DR. WILLIAM S. STREKER

Dr. William S. Streker, F.A.C.P., died suddenly at his summer home at Hyannis, Massachusetts, on July 8, 1945. He had previously shown evidence of arteriosclerotic heart disease.

Dr. Streker was born in Providence on October 11, 1885. He attended public schools in Providence and was graduated in 1908 at the Jefferson Medical College of Philadelphia. He took postgraduate work in internal medicine at the Harvard Medical School and at the Peter Bent Brigham and Massachusetts General Hospitals. In 1931 he became a Fellow of the College. At the time of his death he was Physician-in-Chief at the St. Joseph's Hospital and Consultant at the State Sanatorium at Wallum Lake. He was a diplomate of the American Board of Internal Medicine.

Dr. Streker was President of the Providence Medical Association in 1936. In this capacity he served the community particularly well as he initiated certain changes in the organization which have been of lasting benefit.

He is survived by his wife and four brothers, two of whom are physicians and one a dentist, as well as by three sisters, two of whom are graduate nurses. Throughout his professional career he proved himself to his many patients always a kindly, tactful physician and a faithful friend.

ALEX. M. BURGESS, M.D., F.A.C.P.,
Governor for Rhode Island

DR. JOHN C. GRILL

John C. Grill, M.D., F.A.C.P., Milwaukee, Wisconsin, died of a cerebral hemorrhage on March 17, 1945, at the age of 52. His death has not previously been recorded in this journal. Dr. Grill was born in Vienna, Austria, August 25, 1892. He attended the State Gymnasium at Vienna and received his medical degree from the University of Vienna. He had been Professor and Director of the Department of Pathology at Marquette University School of Medicine, Milwaukee, for several years. He was Director of Laboratories at the Milwaukee County Hospital and Pathologist at St. Mary's and St. Joseph's Hospitals, Milwaukee.

Dr. Grill was a member of the Milwaukee County Medical Society, Wisconsin State Medical Society, American Association of Pathologists and Bacteriologists, American Society of Clinical Pathologists, and the Central Society for Clinical Research. He was a Fellow of the American Medical Association and a former President of the Milwaukee Pathological Society. He was a Diplomate of the American Board of Pathology, and had been a Fellow of the American College of Physicians since 1938.

DR. WILLIAM WALLACE HALL

William Wallace Hall, M.D., F.A.C.P., Watertown, New York, died January 3, 1945, but his death has not previously been recorded in these

columns. Dr. Hall was born at Addison, Steuben County, New York, January 26, 1887. He received his B.S. degree in 1913 and his M.D. degree in 1917 from Syracuse University. He had done postgraduate work at Harvard Medical School, and at the time of his death was Chief of the Medical Service, House of the Good Samaritan, Watertown. Dr. Hall was a member and past President of the Jefferson County Medical Society; a member of the New York State Medical Society, and American Diabetes Association; a Fellow of the American Medical Association; and a Fellow, since 1931, of the American College of Physicians.

DR. HENRY IRWIN KLOPP

Henry Irwin Klopp, M.D., D.Sc., F.A.C.P., Allentown, Pa., died March 7, 1945, but his passing has not previously been recorded in this journal. Dr. Klopp was born at Stouchsburg, Berks County, Pa., in 1870. He attended Albright College, and graduated in medicine from Hahnemann Medical College of Philadelphia in 1894. He interned at the Reading Homeopathic Hospital.

Early in his career Dr. Klopp entered upon the specialty of psychiatry and served successively as Assistant Physician, Assistant Superintendent, and Acting Superintendent of the Westboro (Mass.) State Hospital. He was Superintendent and Physician-in-Chief of the Allentown State Hospital. He was Professor of Mental Diseases, Department of Neurology and Psychiatry, Hahnemann Medical College and Hospital of Philadelphia. Dr. Klopp was a Diplomate of the American Board of Psychiatry and Neurology, a member of the Lehigh County Medical Society, Lehigh Valley Homeopathic Medical Society, Philadelphia Psychiatric Association, Pennsylvania State Homeopathic Medical Society, Association of Medical Superintendents for Mental Disease, and American Psychiatric Association; in 1940–41 he was President of the Pennsylvania Psychiatric Society. He had been a Fellow of the American College of Physicians since 1923, and more recently became a Life Member.

DR. FERGUS OLAMH MAHONY

Fergus Olamh Mahony, M.D., F.A.C.P., El Dorado, Arkansas, died February 6, 1945, aged 65 years. He was born in El Dorado, July 30, 1879, attended the University of Arkansas, and received his medical degree in 1908 from Tulane University of Louisiana School of Medicine. He returned to his alma mater frequently in succeeding years for postgraduate study. He was for many years Surgeon, Missouri Pacific Railroad. From 1921 to 1927 he was El Dorado City Health Officer, and from 1920 to 1929, Union County Health Officer. He had for many years been Chief of Staff, Warner-Brown Hospital. He was a former President of the Arkansas State Board of Health. Dr. Mahony had been honored with the Presidency

of the Arkansas State Medical Society and the Union County Medical Society. He was a member of the Southern Medical Association, a Fellow of the American Medical Association, and had been a Fellow of the American College of Physicians since 1930.

DR. THOMAS WILLETT

Dr. Thomas Willett (Associate), West Allis, Wisconsin, died of myocardial fibrosis, February 25, 1945. He was born in 1877 and graduated in 1903 from the Wisconsin College of Physicians and Surgeons. He had been formerly associated with the Public Health Service Reserve and served overseas during World War I as Lieutenant Colonel, Medical Reserve Corps, U. S. Army. At one time Dr. Willett was Medical Director of the Milwaukee County Hospital for Tuberculosis, and Clinical Director of the Milwaukee South Side Children's Clinics. He was Director of the Milwaukee County Bank at West Allis.

Dr. Willett was a member of the County and State Medical Societies and the Milwaukee Academy of Medicine. He was a Fellow of the American Medical Association, and had been an Associate of the American College of Physicians since 1927, having become an Associate before it became compulsory to qualify for advancement to Fellowship in any particular period. It is regretted that an earlier obituary could not be obtained for record in these columns.

DR. BERNARD ISAAC COMROE

Bernard Isaac Comroe, M.D., F.A.C.P., died suddenly at his home in Philadelphia on September 14, 1945, at the age of 38. Born in York, Pa., in 1906, he entered the University of Pennsylvania at the age of 15 and graduated from its Medical School in 1929. His undergraduate career was one of distinction and brilliance. The promise shown there was abundantly fulfilled in his subsequent short life. He filled an important place in the faculty of his alma mater and was known widely as a student of his chosen specialty: arthritis. Among his numerous publications were two well known textbooks: "Internal Medicine and Dental Practice" and "Arthritis and Allied Conditions." He will be long thanked by the graduates of the University of Pennsylvania who served in the Armed Forces for a little bulletin of Philadelphia news which he prepared and sent them. He was a member of a number of societies and organizations. These included Fellowship since 1937 in the American College of Physicians.

The American College of Physicians has sustained a real loss in the death of this very able and promising young physician. Our sympathy goes to all of his family but particularly to his father, Dr. Julius Comroe, Sr., of York, Pa., who is also a Fellow of the American College of Physicians.

THOMAS M. MCMILLAN, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

DR. ALEXANDER HAMILTON STEWART

Alexander Hamilton Stewart, M.D., F.A.C.P., Harrisburg, Pa., died on July 31, 1945. Dr. Stewart was born in Plumville, Indiana Co., Pa., on July 22, 1880, and was graduated from the University of Pittsburgh School of Medicine in 1907. After his internship in the Columbia Hospital, Wilkinsburg, Pa., and postgraduate work at Harvard University and the Cleveland Clinic, he returned to his home, where for many years he was a member of the medical staff of the Indiana Hospital and Medical Director of Indiana County. He was Secretary and later President of the Indiana County Medical Society. In the Pennsylvania State Medical Society, Dr. Stewart held important and responsible positions, having been Chairman of the Public Health Legislation Committee and formerly a member of the Board of Trustees. Dr. Stewart had been a Fellow of the American College of Physicians since 1926. Dr. Stewart is best known through his work in the Pennsylvania State Department of Health, in which he served a number of years. In 1939 he was made Deputy Secretary of Health. Later he was appointed Secretary of Health and held the latter important position at the time of his untimely death.

THOMAS M. MCMILLAN, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania